OncoLog
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Algorithm for Treating Advanced Ovarian Cancer Increases Complete Resection Rate

By Sarah Bronson

Most ovarian cancers have spread beyond the ovary by the time they are diagnosed, and they often recur even after responding to primary treatment. Researchers at The University of Texas MD Anderson Cancer Center aim to improve patient outcomes by changing the standard approach to newly diagnosed advanced ovarian cancer.

At MD Anderson, laparoscopy is used to assess the resectability of ovarian cancer in patients with no evidence of extra-abdominal metastases. Here, involvement is seen near the pelvic peritoneum (left) and the uterus (right). Image courtesy of Dr. Alpa Nick.

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Algorithm for Treating Advanced Ovarian Cancer

[Continued from **page 1**]

> **"There are several areas of opportunity to improve the up-front management of advanced ovarian cancer.""**
>
> **– Dr. Shannon Westin**

"There are several areas of opportunity to improve the up-front management of advanced ovarian cancer. If we can identify the patients who need surgery first and those who need chemotherapy first, that can change our practice. We're also conducting trials that will help us identify new agents of interest for these patients in the up-front setting," said Shannon Westin, M.D., an assistant professor in the Department of Gynecologic Oncology and Reproductive Medicine.

Need for macroscopically complete resection

Patients with newly diagnosed advanced ovarian cancer with no evidence of extra-abdominal metastases typically undergo a combination of chemotherapy and surgery to debulk or completely remove the primary and metastatic tumors, but whether chemotherapy or surgery should be given first remains a matter of debate. Although a recent clinical trial suggested that the chemotherapy-first and surgery-first approaches lead to similar survival times in patients with advanced ovarian cancer, the broad applicability of those results has been questioned. And some ovarian cancer specialists maintain that the choice of up-front treatment can influence survival. "Selecting the subgroup of patients that will likely benefit from up-front surgery remains a diagnostic dilemma," said Alpa Nick, M.D., an assistant professor in the Department of Gynecologic Oncology and Reproductive Medicine.

Dr. Nick explained that several studies showed that patients in whom macroscopically (grossly) complete resection of the ovarian cancer was achieved by cytoreductive surgery survived longer than those with macroscopically evident disease remaining after the surgery. Therefore, increasing the rate of complete resection is expected to lengthen survival.

If the likelihood of achieving grossly complete resection through up-front surgery could be predicted before treatment begins, then the overall treatment approach could be personalized. Patients for whom up-front surgery is likely to eradicate all grossly visible cancer could receive surgery first, and patients unlikely to attain a grossly complete resection with up-front surgery could receive chemotherapy first to increase the likelihood of a complete resection later.

Predicting which patients will have a grossly complete resection before surgery is performed can be difficult. Imaging-based predictors, such as whether a patient has liver or lung metastases on computed tomography, can reliably reveal unresectable disease but cannot accurately predict which ovarian tumors can be completely resected. To date, the most accurate method for assessing the resectability of advanced ovarian cancer has been laparoscopy. Hence, researchers at MD Anderson have implemented a new algorithm that uses laparoscopic findings to determine the best course of treatment for patients with advanced ovarian cancer.

Treatment algorithm

As part of an MD Anderson program to accelerate the discovery and implementation of new treatments for breast and ovarian cancers, clinicians have focused on improving the rate of cytoreductive surgeries that result in

Genetic Testing in High-Grade Ovarian Cancer

Because close to 20% of patients with high-grade serous ovarian cancer—with or without a family history of cancer—have oncogenic mutations, current National Comprehensive Cancer Network guidelines recommend that all patients with high-grade serous ovarian cancer undergo genetic testing for *BRCA1* and *BRCA2* mutations. Therefore, the MD Anderson "moon shot" program for breast and ovarian cancer aims to offer universal testing for patients with high-grade ovarian cancer and to identify at-risk family members. Since patients with germline *BRCA* mutations are more likely than other patient populations to respond to PARP inhibitors, Dr. Westin will be leading several clinical trials in which patients with ovarian cancer and *BRCA* mutations will be treated with PARP inhibitors. For more information about MD Anderson's moon shot programs, visit www.cancermoonshots.org. ■

The above algorithm is used at MD Anderson to determine the treatment course for patients with advanced ovarian cancer. Patients considered candidates for cytoreductive surgery (CRS) first undergo diagnostic laparoscopy, during which two surgeons independently determine the resectability of the disease using a predictive index value (PIV). Thus a consensus is reached about whether a patient is more likely to benefit from up-front treatment with CRS or neoadjuvant chemotherapy (NACT). Adapted with permission from Macmillan Publishers Ltd: Nick AM, et al. Nat Rev Clin Oncol. *2015;12:239–245.*

grossly complete resections in patients with advanced ovarian cancer. In April 2013, the Gynecologic Oncology Clinic at MD Anderson implemented a quality improvement initiative in which all surgeons agreed to perform diagnostic laparoscopy before attempting cytoreductive surgery in all patients believed to have advanced ovarian cancer on the basis of clinical assessment and computed tomography.

During the laparoscopy, two surgeons independently score the extent of metastatic cancer using an index for disease distribution in the abdomen. The index, created by Anna Fagotti, M.D., and colleagues at Catholic University of the Sacred Heart in Italy, assigns a score of 0 (absent) or 2 (present) for each of seven parameters: unresectable peritoneal carcinomatosis, widespread diaphragmatic disease, infiltrating mesenteric disease, need for potential bowel resection, liver surface involvement, obvious neoplastic involvement of the gastric wall, and supracolic omental disease. According to the Anderson algorithm, a total score below 8 means the disease is resectable, and a score of 8 or higher means the disease is not currently resectable.

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If both surgeons score the cancer as resectable during the laparoscopy, then the patient receives surgery followed by chemotherapy. If both surgeons score the cancer as unresectable, then the patient receives three cycles of neoadjuvant chemotherapy followed by surgery. If the surgeons disagree, then a third surgeon is consulted.

This algorithm differs from previous practice in a few notable ways. Although laparoscopy has been used to determine resectability before, its use before cytoreductive surgery is not currently a standard practice in the United States; instead, the decision of whether to use surgery or chemotherapy first might be made on the basis of clinical assessment. The use of two surgeons to assess the extent of disease during the laparoscopy helps maximize the success rate of the surgery by ensuring that no patient whose disease is too extensive undergoes up-front surgery. Finally, the use of grossly complete resection as an endpoint, in keeping with evidence suggesting that grossly complete resection significantly contributes to longer survival, contrasts with previous definitions of opti-

[Continued from **page 3**]

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– Dr. Alpa Nick

mal cytoreduction as resecting all nodules that are larger than 1 cm or larger than 2 cm.

So far, the new algorithm has, as predicted, improved rates of macroscopically complete resection in patients treated for advanced ovarian cancer. In the patients treated with surgery before chemotherapy, the rate of complete resection dramatically increased, from 20% before April 2013 to almost 90% after the implementation of the algorithm. Similarly, the complete resection rate increased from 60% to almost 80% in patients treated with chemotherapy before surgery. Although it is too soon to tell whether these patients also survive longer, their high rates of complete resection are expected to improve their survival times.

Furthermore, the use of the new algorithm has not affected the patients' time to chemotherapy, a quality measure for ovarian cancer care. Dr. Nick said, "We closely track patient outcomes to ensure that patients are able to begin postoperative treatment in a timely fashion. Thus far, we have not seen any delay in the start of chemotherapy. In fact, the time to chemotherapy has actually decreased in the patients treated with chemotherapy first."

Clinical trials with the Anderson algorithm

Researchers at MD Anderson are also using the Anderson algorithm along with new systemic treatments in patients with advanced ovarian cancer. Dr. Westin is leading a series of clinical trials using a novel trial design called the "window of opportunity," which refers to the time between laparoscopic evaluation and cytoreductive surgery in patients scheduled to undergo surgery before chemotherapy. "We're using the time between the laparoscopy and the surgery to add new therapies," Dr. Westin said. "Standard chemotherapy for ovarian cancer, with paclitaxel and carboplatin, frequently leads to complete responses, but the cancer often recurs later. So we're adding different agents into that up-front setting to maximize the early response and keep the cancer from coming back."

In the window-of-opportunity trials, patients whose laparoscopy shows advanced ovarian cancer that can be completely resected with up-front surgery are given novel agents during the 7–10 days before the surgery. The first such trial will give these patients a short course of the poly(ADP-ribose) polymerase (PARP) inhibitor BMN 673 before surgery. Researchers will then compare tumor tissue taken at the time of the laparoscopy with tumor tissue taken at the time of the cytoreductive surgery, immediately after the short treatment. Dr. Westin said, "These trials are very information rich because they show us the effects these drugs have on tumor tissue that has never been treated before. Once we identify drugs that seem to produce a response in patients with specific characteristics, we can treat those patients and subsequent patients who have those characteristics with those new agents combined with standard chemotherapy after their surgery and possibly get better outcomes than what we're currently achieving."

In another line of trials, patients with advanced ovarian cancer who will receive neoadjuvant chemotherapy will be given experimental agents along with the cytotoxic chemotherapy drugs. Dr. Nick is developing one such trial, in which patients will receive neoadjuvant chemotherapy combined with the immune checkpoint inhibitor MK-3475. To assess the effects of these combination treatments on tumor tissue, the tissue taken before treatment during the laparoscopy will be compared with tissue taken at the time of the cytoreductive surgery.

Another area of interest for researchers is maintenance therapy. "Advanced ovarian cancer tends to recur. If there's a drug that these patients could take after primary treatment that would keep the cancer away, that would be a huge benefit," said Dr. Westin. "We are considering certain targeted agents, like PARP inhibitors and antiangiogenic agents, that may work as maintenance therapy. Some of our trials in this area are looking at which drugs to give which patients as maintenance and at what dosages those drugs should be given."

Long-term goals

Clinicians in the Department of Gynecologic Oncology and Reproductive Medicine think the Anderson algorithm could change the standard approach to advanced ovarian cancer. Dr. Nick and Anil Sood, M.D., a professor in the Department of Gynecologic Oncology and Reproductive Medicine, have presented the algorithm at institutions in the MD Anderson Network, at other tertiary care centers in the United States, and at institutions worldwide throughout MD Anderson's Global Academic Programs Sister Institution Network. Dr. Nick

"We closely track patient outcomes to ensure that patients are able to begin post-operative treatment in a timely fashion. Thus far, we have not seen any delay in the start of chemotherapy."

– Dr. Alpa Nick

said that these other groups are highly interested in implementing the algorithm in their practices.

MD Anderson researchers also hope to gain knowledge of the molecular and genomic profiles of ovarian cancer over the course of treatment. Tissue changes after neoadjuvant or window-of-opportunity treatment with new systemic agents should help reveal which tumors respond best to which drugs, and molecular changes between the primary tumor and metastatic sites throughout the abdomen are expected to shed light on ovarian cancer biology and evolution. ■

FOR MORE INFORMATION

Dr. Alpa Nick *713-563-6658*
Dr. Shannon Westin *713-794-4314*

To learn more about ongoing clinical trials for ovarian cancer treatment, visit www.clinicaltrials.org and select "View studies by cancer type."

FURTHER READING

Nick AM, Coleman RL, Ramirez PT, et al. A framework for a personalized surgical approach to ovarian cancer. *Nat Rev Clin Oncol.* 2015;12:239–245.

Clinical Trials Explore Systemic Treatments for Brain Metastases from Breast Cancer

By Bryan Tutt

Brain metastases from breast cancer are difficult to treat because many of the systemic drugs that are effective against breast cancer cannot cross the blood-brain barrier. But researchers at The University of Texas MD Anderson Cancer Center are working to overcome this challenge and are testing new systemic treatments for breast cancer brain metastases in three clinical trials.

With the current standard of care, a patient's overall survival is rarely extended beyond 18 months. The goal of clinicians and scientists at MD Anderson is to find treatments that will prolong survival and preserve quality of life for patients with brain metastases from breast cancer.

Standard treatments

Brain metastases from breast cancer typically are treated with surgical excision, stereotactic radiation therapy, and/or whole-brain irradiation.

"If the patient has only a few metastases in the brain, we use either surgical excision or stereotactic radiation therapy followed by whole-brain irradiation," said Nuhad Ibrahim, M.D., a professor in the Department of Breast Medical Oncology. "However, if there are multiple or diffuse metastases in the brain, whole-brain irradiation is the modality of choice." Since whole-brain irradiation may result in decreased neurocognitive function, the treatment is deferred in some patients until evidence of disease progression is seen.

Although systemic therapy with cytotoxic or targeted agents can control breast cancer metastases outside the brain for extended periods, the blood-brain barrier limits the effectiveness of these drugs against brain metastases by preventing the drugs' delivery into the brain parenchyma.

"The role of systemic therapy remains very limited in the management of brain metastases," Dr. Ibrahim said. "The challenge is to develop drugs that are able to cross the blood-brain barrier and have an effect on the tumor."

Dr. Ibrahim is the principal investigator of three clinical trials of systemic treatments aimed at overcoming this challenge.

"[W]e hope the trials will also add to our understanding of the biology of metastasis to the brain."

– Dr. Nuhad Ibrahim

Clinical trials

TPI 287

A phase I trial of the tubulin inhibitor TPI 287 is currently enrolling breast

Systemic Treatments for Brain Metastases from Breast Cancer

[Continued from **page 5**]

cancer patients whose brain metastases progressed after standard therapy with surgery and/or radiation therapy. To participate in the study, which is available only at MD Anderson, patients must have new brain metastases in untreated areas.

"TPI 287 is the first drug in its class, but its mechanism of action is like that of taxanes," Dr. Ibrahim said.

Preclinical studies have shown that TPI 287 crosses the blood-brain barrier and is active against both taxane-sensitive and taxane-resistant tumors. Preclinical studies have also shown the drug to be active against triple-negative breast cancer, which has a high propensity to metastasize to the brain. And one clinical study found that TPI 287 had clinical activity against glioblastoma, further proving its ability to cross the blood-brain barrier.

Neratinib

MD Anderson is participating in a multi-institutional phase II trial of the oral tyrosine kinase inhibitor neratinib (also called HKI-272) in patients with human epidermal growth factor receptor 2 (HER2)–positive breast cancer that has metastasized to the brain.

The nonrandomized trial, which is enrolling treatment-naïve patients as well as patients whose brain metastases progressed after radiation therapy and/or surgery, has three treatment arms. Patients with progressive brain metastases are assigned to receive neratinib only or neratinib and capecitabine. Patients whose disease is amenable to surgery are treated with neratinib for 7–10 days before surgery and then indefinitely after surgery unless disease progression or severe toxic effects occur. Patients in any treatment arm who have progressive metastatic disease outside the central nervous system may also receive trastuzumab.

Neratinib has been shown in previous clinical trials to be active against HER2-positive breast cancer, as has the combination of neratinib and capecitabine. In preclinical studies, both capecitabine and neratinib have been shown to cross the blood-brain barrier.

"The challenge is to develop drugs that are able to cross the blood-brain barrier and have an effect on the tumor."

– Dr. Nuhad Ibrahim

ANG1005

Another multi-institutional phase II trial is evaluating ANG1005 in patients with recurrent brain metastases from breast cancer. ANG1005 comprises three molecules of paclitaxel linked to a 19-amino-acid peptide chain that binds to a receptor called LRP-1. LRP-1's expression on leptomeningeal cells allows ANG1005 to cross the blood-brain barrier, and the receptor's expression on cancer cells enhances the delivery of paclitaxel to the tumor.

"ANG1005 has been shown to be active against leptomeningeal metastases of breast cancer, and therefore this study accepts patients who have leptomeningeal disease in addition to those with parenchymal brain metastases," Dr. Ibrahim said. "We think this might prove to be one of the very few instances where a cytotoxic compound is active against leptomeningeal disease as well as parenchymal disease."

The current study was initiated on the basis of preliminary data from other clinical trials, which indicated that ANG1005 was active against glioblastoma and brain metastases from breast and lung cancers. "We are very excited about this potential role for this drug," Dr. Ibrahim said.

Increasing patients' options

All three clinical trials are examining the objective response rate; the trials will also assess progression-free and overall survival and the drugs' safety and tolerability. Although early results of the trials are not yet available, Dr. Ibrahim is optimistic that patients in the studies will benefit from the treatments.

The prospect of adding systemic drugs to the treatment options available for patients with brain metastases from breast cancer is promising, Dr. Ibrahim said. "Surgery and radiation therapy are effective modalities of treatment for breast cancer patients with brain metastases," he said. "However, the duration of benefit is always limited. These trials offer other options for these patients, and we hope the trials will also add to our understanding of the biology of metastasis to the brain. This knowledge could lead to treatments that could control existing metastatic disease or prevent the occurrence of brain metastases in breast cancer patients at high risk." ■

FOR MORE INFORMATION

Dr. Nuhad Ibrahim.....713-792-2817

To learn more about the ongoing clinical trials of systemic therapy for patients with brain metastases from breast cancer, visit www.clinicaltrials.org and select study No. 2010-0198, 2013-1007, or 2014-0854.

Tips for Communicating with Health Care Providers

Preparing for appointments can help you get the answers you need

Whether you are getting a regular checkup or treatment for a serious illness, the best doctor-patient experience requires effective communication. As health care appointments continue to feel shorter and more rushed, it is important to communicate freely and clearly to receive the best care possible in the time available. Often, however, patients do not feel comfortable speaking with health care providers or do not know what to ask and know how to ask it. Here, we present some tips on how to communicate effectively with your health care providers.

Come prepared

Your correct diagnosis or treatment may depend on the quality of the information you can share with your doctor about what you have been experiencing.

Keep notes of your symptoms, like unusual body changes or reactions. Be specific about the start dates, lengths of time, and changes in intensity of any symptoms. Keep an up-to-date list of the current prescription or over-the-counter medications you take. Be sure to include any complementary or alternative medicines and supplements you use, such as herbs, vitamins, and homeopathic remedies. These might contribute to your symptoms or interfere with any prescribed medications.

Maintain your own medical history (past symptoms or diagnoses, major surgeries, and current conditions), and make notes of your general family medical history (for example, knowing that conditions such as high blood pressure, cancer, or diabetes run in your family). Bring these lists with you to your appointments to share with your doctor, particularly if it is a first visit.

Be active

Consider yourself an active member of your health care team rather than a passive patient. Learn about your health concerns and illnesses. Try to gather all the information you need to make informed decisions about your health.

Ask questions

Another way to be active and prepared is to write down any questions or concerns you have. List or mark them in order of importance. Refer to the list during the appointment to avoid forgetting to ask something. Do not be afraid to ask these questions or any other questions that may arise. Your health care providers want you to understand any conditions you may have and any proposed treatments.

Get clarification

If you do not understand a concept or procedure completely, ask your doctor to clarify. Perhaps he or she needs to use less technical language. It is important that you have an understanding of your care that is satisfactory to you.

In your own words, repeat back what your doctor explains to you to make sure you understand. This is a great opportunity to confirm what you know and get clarification on what you don't fully grasp.

Share other communication needs

Let your doctor know if you have vision or hearing problems so that he or she can tailor communication to your needs. For example, you may need your doctor to face in a specific direction when speaking to you or provide informational material published in large print or in a different language.

Bring additional support

You might want to bring a family member or friend to accompany you on doctor's appointments. This person can take notes for you, be an additional listener, remember information you might forget, and provide support.

Get to know your care team

Familiarize yourself with your care team or the doctor's office staff. The nurses and physician assistants are knowledgeable and important members of your health care team who can provide basic information and guidance about your care. Ask about who, besides your main doctor, can answer additional questions and how members of your health care team may be reached by phone or email.

Building your doctor-patient relationship may be a gradual process, but it is an important one. Providing accurate information and making sure you understand your doctor's instructions and advice can help you get the best care possible. Knowing your care team, bringing support, being prepared, and asking questions all can help you get the most out of your time with your health care team. ■

— U. Arizor

FOR MORE INFORMATION

- *Talk to your physician*
- *Visit www.mdanderson.org/icare and click on the link: "For Patients and Families"*
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IN BRIEF

Sentinel Lymph Node Mapping Identifies Node-Positive, High-Risk Endometrial Cancer

Sentinel lymph node (SLN) mapping accurately identifies node-positive, high-risk endometrial cancer, the preliminary results of an ongoing study at The University of Texas MD Anderson Cancer Center indicate.

In women with high-risk endometrial cancer, the current standard of care for initial treatment and staging is hysterectomy plus complete pelvic and para-aortic lymphadenectomy. However, the surgery carries a risk of intraoperative and postoperative morbidities. SLN mapping, in which dye is injected into the cervix to help surgeons locate the SLNs and remove them for biopsy, is less invasive than the standard approach.

"If we could identify patients with positive nodes yet not have to do a full lymphadenectomy, we could potentially decrease the morbidity for patients and still appropriately determine postoperative therapy," said Pamela Soliman, M.D., an associate professor in the Department of Gynecologic Oncology and Reproductive Medicine.

"If we continue to see such promising results, sentinel lymph node mapping could change the overall management of endometrial cancer."

– Dr. Pamela Soliman

Dr. Soliman is the principal investigator of the ongoing study, whose purpose is to compare SLN mapping and positron emission tomography/computed tomography (PET/CT) for detecting lymph node metastases. In the single-institution prospective study, patients with high-risk, grade 3 endometrial cancer undergo preoperative PET/CT and intraoperative SLN mapping followed by standard treatment with hysterectomy and complete lymphadenectomy.

Of 60 evaluable patients, at least one SLN was identified in 56 (93%), and bilateral SLNs were identified in 37 (62%). Each patient who had a disease-positive lymph node on final pathology had at least one positive SLN, for a sensitivity of 100%. The false-negative rate was 0%.

"If we continue to see such promising results, sentinel lymph node mapping could change the overall management of endometrial cancer, much like we have seen it do in other diseases," Dr. Soliman said. She added that the PET/CT data are still being reviewed.

Dr. Soliman and her colleagues presented their findings at the Society of Gynecologic Oncology's Annual Meeting on Women's Cancer in Chicago in March. ■

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