Small Cell Lung Cancer Studies May Increase Treatment Options

By Bryan Tutt

Despite advances in treating many cancers, the standard treatment of small cell lung cancer has remained unchanged for decades. But researchers at The University of Texas MD Anderson Cancer Center are exploring several new approaches to treat small cell lung cancer.

Among the most promising of these approaches is the use of poly(ADP-ribose) polymerase (PARP) inhibitors, a class of drugs already used against other types of cancer.

The problem

The standard treatment for small cell lung cancer has remained largely unchanged since the 1980s. Newly diagnosed patients with disease limited to one region of the chest typically receive radiation therapy with carboplatin and etoposide, while those with more extensive disease receive chemotherapy alone. In most patients, the tumors initially shrink markedly but start growing again in 4–6 months.

The targeted agents that are effective against many types of cancer, including non–small cell lung cancer, are ineffective against small cell lung cancer, said John Heymach, M.D., Ph.D., a professor in and chair of the Department of Thoracic/Head and Neck Medical Oncology. “In non–small cell

Shrinkage of small cell lung cancer (arrows) can be seen in computed tomography scans taken before (left) and after 4 weeks of treatment with the PARP inhibitor veliparib and the cytotoxic drug temozolomide (right). Image courtesy of Dr. Lauren Byers.
lunge cancer, there’s often a single driver oncogene that we can target with new drugs,” he said. “But small cell lung cancer is wired differently. Small cell lung cancer doesn’t seem to have these driver oncogenes. We think what drives it is the loss of tumor suppressor genes RB1 and TP53.”

**PARP inhibitors**

To identify new therapeutic targets for small cell lung cancer, researchers led by Lauren Byers, M.D., an assistant professor in the Department of Thoracic/Head and Neck Medical Oncology, conducted a proteomic analysis of both small cell and non–small cell lung cancer cells to systematically assess the activation of critical intracellular signaling pathways. “Because there haven’t been any approved targeted drugs for small cell lung cancer, we wanted to identify differences between small cell and non–small cell lung cancer that could help us identify new drugs that could work against small cell lung cancer,” Dr. Byers said.

The researchers found that PARP1, an enzyme involved in DNA repair, was expressed at high levels in small cell lung cancer cells. Dr. Heymach said these high levels may be related to the loss of RB1 and TP53.

The discovery of elevated PARP1 expression in small cell lung cancer was exciting because drugs that inhibit PARP proteins are available; such drugs are sometimes used to treat breast or ovarian cancers in patients with BRCA1 or BRCA2 mutations. “The idea is that since tumors with BRCA mutations already have a defect that inhibits their ability to repair DNA damage, the PARP inhibitor will further impair the cells’ ability to repair DNA damage and cause the cells to die,” Dr. Byers said. When further experiments showed that PARP inhibitors used to treat breast and ovarian cancers also killed small cell lung cancer cells, Dr. Byers said, “We saw the opportunity to take our observation into the clinic quickly.”

Dr. Byers is leading or participating in three ongoing clinical trials of PARP inhibitors for lung cancer treatment—one for non–small cell and two for small cell lung cancer. Currently enrolling patients with relapsed or refractory small cell lung cancer is a multicenter phase II trial of the PARP inhibitor veliparib (previously called ABT-888) with the cytotoxic drug temozolomide. Patients in the study are randomly assigned to receive temozolomide with veliparib or placebo.

The study’s goal is to learn whether the addition of veliparib will extend progression-free survival. “The idea is that the cytotoxic drug causes DNA damage in the cancer cells, and the PARP inhibitor prevents the cancer from repairing the damage,” Dr. Byers said. “It’s still early, but we’re excited by some of the results we’re seeing.”

The second study of PARP inhibitors in small cell lung cancer is a first-in-human study of the PARP inhibitor BMN 673. The goals of this study are to find the maximum tolerated dose of BMN 673 and to assess the drug’s efficacy in patients with advanced or recurrent solid tumors. The trial recently reached its enrollment goal.
Preliminary results of the BMN 673 trial were presented last year at the annual meeting of the American Society of Clinical Oncology. Of 11 evaluable patients with small cell lung cancer, 2 had a complete response according to the Response Evaluation Criteria in Solid Tumors and another 6 had either a partial response or stable disease lasting longer than 8 weeks. "The data were preliminary, but they were encouraging," Dr. Byers said. "Patients seemed to benefit from the drug in the second-line setting."

Even as the clinical trials progress, Dr. Byers continues to study small cell lung cancer in the laboratory. Because BRCA mutations have not been linked to small cell lung cancer, Dr. Byers and other researchers believe that PARP inhibitors work differently in small cell lung cancer than in breast and ovarian cancers. "Our lab is trying to find out which characteristics of small cell lung cancer make it particularly sensitive to these targeted drugs," Dr. Byers said, adding that a biomarker has not yet been found to indicate which patients with small cell lung cancer are most likely to respond to PARP inhibitors. "We want to understand which patients will get the most benefit from these drugs."

The next step in PARP inhibitor research will be testing the drugs with front-line treatments. Dr. Byers and her colleagues are planning a clinical trial in which the PARP inhibitor veliparib will be given with the standard initial regimen of carboplatin and etoposide plus radiation therapy for patients with extensive stage small cell lung cancer.

**Other research**

Like PARP inhibitors, antiangiogenic drugs have been used effectively against other types of cancer and are now under investigation for the treatment of small cell lung cancer. Dr. Heymach thinks that antiangiogenic drugs such as vascular endothelial growth factor (VEGF) inhibitors may be effective against small cell lung cancer when combined with other agents. A clinical trial of the PARP inhibitor olaparib and the VEGF inhibitor cediranib for the treatment of advanced small cell lung cancer is being developed at MD Anderson.

Another promising avenue of research, still in its early stages, is to engineer T cells using chimeric antigen receptors (see “Sleeping Beauty’ Technique Modifies T Cells to Treat B Cell Malignancies,” *OncoLog*, May 2014) so that the T cells recognize small cell lung cancer. MD Anderson researchers including Laurence Cooper, M.D., Ph.D., a professor in the Division of Pediatrics, and Warren Denning, Ph.D., a postdoctoral fellow in the Department of Thoracic/Head and Neck Medical Oncology, are modifying T cells so that they bind to CD56, which is expressed on small cell lung cancer cells.

“We’re also hoping that immunotherapy will be effective against small cell lung cancer, but there aren’t any data yet,” Dr. Heymach said. Among the researchers investigating this approach are James Welsh, M.D., an associate professor in the Department of Radiation Oncology, and Kathryn Gold, M.D., and Ermiria Massarelli, M.D., Ph.D., both assistant professors in the Department of Thoracic/Head and Neck Medical Oncology. Dr. Heymach believes that immunotherapy drugs may be most effective after front-line chemotherapy has minimized a patient’s tumor burden. A study is being planned in which patients with advanced small cell lung cancer will receive standard chemoradiation therapy followed by the immunotherapy agent pembrolizumab (also called MK-3475), which targets programmed cell death protein 1.

Dr. Byers hopes that these other avenues of research will progress as rapidly as her group’s PARP research has. "We published the paper of our initial discovery of PARP in small cell lung cancer in 2012. That’s a fast turnaround time for translational medicine, to go from a discovery published in 2012 to clinical results reported in 2014."

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**the cytotoxic drug causes DNA damage in the cancer cells, and the PARP inhibitor prevents the cancer from repairing the damage.**

– Dr. Lauren Byers

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**FURTHER READING**


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**FOR MORE INFORMATION**

Dr. Lauren Byers.................713-792-6363
Dr. John Heymach.................713-792-6363

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Improved Maintenance Therapy Promotes Myeloma Patients’ Quality of Life After Stem Cell Transplantation

By Kathryn L. Hale

High-dose chemotherapy followed by autologous stem cell transplantation can prolong survival for patients with multiple myeloma. However, patients remain at a high risk of relapse even after transplantation. Maintenance therapy can extend remission in these patients, and clinical trials at The University of Texas MD Anderson Cancer Center are exploring new maintenance regimens to further improve patients’ outcomes.

Myeloma patients and their physicians must weigh the possible benefit of prolonged remission against the risk of adverse effects from maintenance therapy. “The challenge,” said Jatin Shah, M.D., an associate professor in the Department of Lymphoma and Myeloma, “is finding therapies that are effective at maintaining remission and at the same time are easy for patients to take over a period of years, with a simple regimen and few and mild side effects. The goal is to help patients continue therapy with minimal disruption of their everyday lives.”

Lenalidomide maintenance

Low-dose lenalidomide is the most common maintenance regimen for myeloma patients. Two recent clinical trials showed that low-dose (10 mg) daily oral lenalidomide prolonged remission by 18–24 months after stem cell transplantation compared with watchful waiting. Early data from one of the studies suggested that this therapy also prolongs survival.

To minimize adverse effects and increase the tolerability of maintenance therapy, lenalidomide has usually been given alone. Nevertheless, minor effects such as diarrhea, rash, and fatigue do occur. By far the greatest concern is a second primary cancer, which occurs in 8%–9% of myeloma patients who receive lenalidomide maintenance therapy but in only 3%–4% of those who do not receive it. “While this doubling of risk still means second cancers occur in only a minority of patients,” Dr. Shah said, “it is an important risk that patients have to be aware of.”

Bortezomib and ixazomib

Although low-dose lenalidomide maintenance therapy has been shown to be effective and well tolerated, researchers are looking for ways to further prolong remission and survival after transplantation while minimizing the risk of a second cancer. The combination of lenalidomide with the proteasome inhibitor bortezomib was shown to be effective in patients with newly diagnosed and relapsed myeloma. However, bortezomib can be given only as an injection or infusion, so patients would have to visit the clinic every week or two for an indefinite period if they were to receive the drug as maintenance therapy.

In an effort to improve patient convenience and quality of life, researchers at MD Anderson are currently testing the second-generation proteasome inhibitor ixazomib (also called MLN9708)—which is given orally—in combination with lenalidomide for myeloma maintenance therapy in a clinical trial. “We think that this will be an effective strategy in prolonging remission,” said Dr. Shah, the trial’s principal investigator. “But we don’t know how much improvement we’ll see or what the side effects will be. That’s the reason for the trial.”

Because the focus is on long-term outcomes such as relapse and survival, the investigators are still waiting for results. “What we can say right now,” Dr. Shah said, “is that we have not seen any unusual or unexpected toxic effects in the patients who have begun the therapy. We’re reassured by how well the therapy is tolerated by most patients.”

Dr. Shah said that the all-oral regimen allows patients to work full time, travel, and take part in the activities they enjoy. “They come to the cancer center once a month, they get their pills, and they continue to maintain a good quality of life,” Dr. Shah said. “We’ve seen no limitations for the majority of these patients. It’s very encouraging to see that patients are able to do everything they want to do despite the therapy—and we hope that we’re providing not only increased time in remission but also better quality time.”

Maintenance therapy research continues

Dr. Shah hopes that eventually there will be a marker to identify which patients need maintenance therapy and which do not. “The question is not how to identify patients who will respond to maintenance therapy, since most do, but rather how to identify patients who will do well without the therapy and thus can be spared the potential side effects,” he said. “One of the things we’re looking at is minimal residual disease. Patients who could be shown by special tests to have no minimal residual disease at a deep molecular level, signifying deep remission, might not need maintenance therapy. I think incorporating such a test is the next major step.”
Another question that is yet to be answered is the optimal duration of maintenance therapy. Although some oncologists think that shortening the duration of maintenance therapy would reduce the incidence of second primary neoplasms, Dr. Shah and his colleagues at MD Anderson believe more data are needed. While the use of limited-duration maintenance therapy in some centers may one day provide such data, Dr. Shah said, “Right now, we think that indefinite therapy—continuing the therapy for as long as the patient is still benefiting from and tolerating therapy—is the best way to go.”

Looking toward the future, Dr. Shah and his colleagues at MD Anderson have plans for additional trials to refine myeloma maintenance therapy further. “We expect to use the data from the current ixazomib trial to support a potential phase III trial in which we’ll compare lenalidomide alone with a lenalidomide-ixazomib combination.”

And other trials are in the works at MD Anderson. One planned trial, which will begin later this year, will look at the new monoclonal antibody elotuzumab. Elotuzumab targets a protein called SLAM family member 7, which is expressed on the surface of all myeloma cells in the majority of patients. “Elotuzumab goes after only the myeloma cells,” Dr. Shah said. “In a phase II trial, elotuzumab with lenalidomide delayed relapse by 24–33 months, much longer than the 11 months seen in patients treated with lenalidomide in previous trials who were used as historical controls. This potential doubling or tripling of remission time in a phase II trial is significant.”

Elotuzumab is currently an intravenous formulation, requiring patients to come to the center for treatment weekly at first and then over time transition to monthly treatment. However, Dr. Shah said, “The upside is that elotuzumab is not like standard chemotherapy, so we expect minimal additional side effects besides those from the lenalidomide—a nice benefit. And, considering the earlier results showing a doubling or tripling of survival, we are optimistic about the potential for prolonged remissions we’ll see with the combination in the maintenance setting.”

At this time, no other centers in the United States are offering maintenance regimens with ixazomib or elotuzumab, to Dr. Shah’s knowledge. Dr. Shah said, “We’re very excited that we are able to offer our myeloma patients unique, innovative trials of therapies that may give them a longer, healthier life.”

FOR MORE INFORMATION
Dr. Jatin Shah..........................713-745-6130
jjshah@mdanderson.org
myelomatrial@mdanderson.org

To learn more about the ongoing clinical trial of ixazomib for myeloma maintenance therapy, visit www.clinicaltrials.org and select study No. 2012-0277.
However, the role of primary tumor resection is less clear in the majority of patients, who are asymptomatic at presentation. In patients with metastatic colorectal cancer whose primary tumors are nonobstructive and whose metastatic disease cannot be resected, the National Comprehensive Cancer Network recommends systemic chemotherapy without primary tumor resection. A select but small group of patients may benefit from the surgery as a prophylaxis to prevent primary tumor–related symptoms during chemotherapy. However, noncurative primary tumor resection is associated with morbidity rates of up to 30% and mortality rates of up to 10%. And in many patients with advanced colorectal cancer, noncurative primary tumor resection may in fact preclude the use or delay the start of systemic therapies shown to provide a survival benefit.

“We know that it’s safe to give chemotherapy even with biologics such as bevacizumab to patients with metastatic disease. Yet there’s still controversy about the role of primary tumor resection because of persistent concerns about primary tumor–related complications and because some believe that there’s a survival association,” said George J. Chang, M.D., M.S., an associate professor in the Departments of Surgical Oncology and Health Services Research and the corresponding author of the study’s report. “The purpose of our study was to evaluate the use of primary tumor resection among patients with metastatic colorectal cancer in everyday practice by examining national trends in the proportion of stage IV patients undergoing primary tumor resection.”

New agents bring change
Using the National Cancer Institute’s Surveillance, Epidemiology, and End Results database, Dr. Chang and his colleagues identified more than 64,000 patients who were diagnosed with metastatic colorectal cancer between 1988 and 2010. About two-thirds (67.4%) of these patients underwent primary tumor resection. Factors associated with an increased likelihood of undergoing the surgery included


“[T]here may still be an overutilization of primary tumor resection.”
– Dr. George Chang

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How Hospital Chaplains Help

Chaplains help patients and families deal with emotional and spiritual concerns

Anyone who has been hospitalized with a serious illness knows there is much more to cope with than just one’s physical condition. Hospital chaplains help patients deal with the emotional and spiritual issues that often accompany medical problems.

Spiritual beliefs and illness

Hospital chaplains respect the spiritual beliefs of all patients and family members, not just those affiliated with specific religions.

Spirituality is more than a particular religion, explained the Reverend Carol Dimmett, a staff chaplain at The University of Texas MD Anderson Cancer Center. Rather, she said, “Spirituality is what helps give ultimate meaning to our lives and gives us a sense that there is something larger than ourselves from which we can draw comfort, meaning, hope, and strength.”

Patients’ spiritual beliefs can either help them cope with their illness or add to their burden, Ms. Dimmett said. “Chaplains encourage patients to focus not on what is broken but on what is whole and then to try to nurture that,” she added. “We help people to reconnect to their own belief systems and to strengthen or broaden those beliefs. This can be instrumental in restoring a sense of connection and peace.”

How chaplains help

How chaplains help depends on the patient’s wishes. Chaplains can provide comforting bedside visits or act as liaisons between hospital staff and patients’ families.

Chaplains offer pastoral counseling, support groups, crisis intervention, and prayer support to help patients and their families cope with spiritual or emotional distress, grief, or end-of-life issues.

Empathetic listening is an important skill chaplains bring to patients, allowing the patients to have their painful experiences heard and acknowledged. “Sharing their struggles, sorrows, and joys brings intimacy and healing,” Ms. Dimmett said. “This process can help the patients reestablish connections with their sense of self, with the Divine, and with things that were important to them before their illness.”

In addition, hospital chaplains provide patients’ families with support. This can be particularly helpful if a patient is terminally ill or has died. Chaplains may encourage families to share stories about the patient or to pray together. “Prayer helps people release their emotions,” Ms. Dimmett said. “Gathering around the bed with family and friends—sometimes holding hands and uniting in prayer—helps release grief, sadness, and anger. When the family participates, it provides a way for them to share their feelings and cry openly.”

Most hospital chaplains also lead regular worship services—both interdenominational and interfaith—and can conduct marriages, funerals, and other sacraments.

Chaplains and their training

Ms. Dimmett, like many hospital chaplains, is a board-certified chaplain. This certification requires a graduate degree in theology, additional training in clinical pastoral education, ordination or commissioning by a faith organization, and 2,000 hours of work experience as a provisional or associate certified chaplain. She said that all chaplains at MD Anderson are board certified.

For patients and their families, hospital chaplains help ease the spiritual burdens of serious illness.

“...we help people to reconnect to their own belief systems and to strengthen or broaden those beliefs. This can be instrumental in restoring a sense of connection and peace.”
—The Reverend Carol Dimmett

FOR MORE INFORMATION
- Talk to your physician
- Call MD Anderson’s Department of Chaplaincy and Pastoral Education at 713-792-7184
- Visit the Department of Chaplaincy and Pastoral Education at www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/chaplaincy
Metastatic Colon Cancer
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female sex, age less than 50 years, and being married in addition to cancer-related factors such as having colon (rather than rectal) cancer and having a high-grade tumor.

The researchers found that the annual rate of primary tumor resection decreased 17 percentage points between 1988 and 2010, from 74.5% to 57.4%. The most dramatic decreases, which occurred after 2001, coincided with the timing of the U.S. Food and Drug Administration’s approval of a bevy of systemic and biologic therapies for colorectal cancer. These agents—which include irinotecan, oxaliplatin, capecitabine, bevacizumab, cetuximab, and panitumumab—can be used in the first-, second-, or third-line settings with or without fluorouracil and folinic acid to treat the disease. The agents have been found to prolong survival and to be associated with low rates of primary tumor–related complications. In addition, the agents can be used to shrink borderline resectable disease so that it can be removed with potentially curative surgery.

“Our findings tell us that it is increasingly recognized that chemotherapy may be safely given to patients with intact tumors,” Dr. Chang said.

The researchers also found that despite the decrease in annual rates of primary tumor resection over the study period, the patients’ median 5-year relative survival rate improved during this time, from 8.6% in 1988 to 17.8% in 2009 (2010 survival data were not available).

“We know that it’s safe to give chemotherapy even with biologics such as bevacizumab to patients with metastatic disease. Yet there’s still controversy about the role of primary tumor resection.”

– Dr. George J. Chang

“Although fewer people are getting primary tumors resected, a large proportion of patients with metastatic disease at diagnosis are still having them removed,” Dr. Chang said. “Together with the observation that primary tumor resection was more likely to be performed in younger patients who have colon rather than rectal cancers, this suggests that there may still be an overutilization of primary tumor resection and that careful consideration of the indication for such surgery should be made.”

The study was published in the January issue of JAMA Surgery.

FOR MORE INFORMATION
Dr. George J. Chang .................713-792-6940