Proton Therapy Trials May Provide More Options for Patients with Non–Small Cell Lung Cancer

By Jill Delsigne

Proton therapy offers the potential to deliver a higher radiation dose to lung tumors and a lower dose to healthy tissue than does standard radiation therapy. However, the effectiveness of proton therapy has not yet been documented in clinical trials for patients with non–small cell lung cancer (NSCLC), the most common type of lung cancer. Two ongoing trials of proton therapy aim to demonstrate its effectiveness and may change the standard of care for NSCLC.

Since 2004, the standard treatment for locally advanced (stage II or III), inoperable NSCLC has been concurrent platinum-based chemotherapy and photon-based intensity-modulated radiation therapy (IMRT), usually with a total radiation dose of at least 60 Gy. However, because photons are transmitted via high-energy waves that pass through the tumor, adjacent healthy tissues are often affected, exposing patients to cardiac and pulmonary toxicity.

The radiation dose to healthy lung and heart tissue in NSCLC patients can be reduced by using proton therapy. Unlike photon therapy, proton therapy uses high-energy particles to target tumors; the particles stop at the tumor site and release most of their energy, sparing healthy tissues.

“NSCLC often occurs in smokers who have poor cardiopulmonary reserve, so reducing the total dose of radiation to the lung tissue and heart is critical,” said Quynh-Nhu Nguyen, M.D., an associate professor in the Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center.

Dr. Nguyen, along with Zhongxing Liao, M.D., a professor in the Department of Radiation Oncology, and other colleagues, recently conducted a retrospective study of 134 patients with inoperable stage II or III NSCLC treated with concurrent proton therapy and chemotherapy at MD Anderson.
son. Patients with stage II NSCLC had a median overall survival of 40.4 months, and those with stage III NSCLC had a median overall survival of 30.4 months. Only six of the 134 patients experienced grade 3 toxic effects, and one patient experienced a grade 4 toxic effect.

These promising findings illustrated the need for prospective clinical trials to compare photon and proton therapies head to head. Dr. Nguyen said, “Results from randomized trials are needed to show that proton therapy is effective for patients with NSCLC.” Two such trials—one comparing photon therapy to proton therapy and another evaluating the effectiveness of a simultaneous integrated boost to increase the treatment dose in both photon and proton therapy—are under way at MD Anderson.

Randomized head-to-head trial

Drs. Nguyen and Liao are currently enrolling previously untreated patients with inoperable stage II or III NSCLC in a randomized phase III trial (RTOG 1308) comparing the overall survival durations of patients treated with chemotherapy and concurrent photon therapy to those of patients treated with chemotherapy and concurrent proton therapy. Dr. Nguyen is the institutional principal investigator and Dr. Liao is the national principal investigator for this multicenter trial.

Patients in the trial are randomly assigned to receive either IMRT or passively scattered proton therapy at a total dose of 70 Gy given in daily fractions 5 days per week for 7 weeks (35 fractions); the total dose can be reduced to 60 Gy if treatment planning for the higher dose level does not meet the dose constraints for healthy tissue. “This could be a practice-changing trial,” Dr. Liao said. “Our results may provide level I evidence of the benefits of proton therapy and shape clinical guidelines.”

Simultaneous integrated boost

Dr. Liao is also the principal investigator for a nonrandomized phase I/II trial (2011-1058) in which patients with stage II or III NSCLC receive chemotherapy with IMRT or scanning beam intensity-modulated proton therapy (IMPT). Unlike the randomized phase III trial, both the photon and proton radiation therapy in this trial will include a simultaneous integrated boost to deliver more radiation to the tumor than to the surrounding tissue. “Traditionally, the radiation treatment volume for both photon and proton therapy includes a margin of 1.3–1.5 cm around the tumor, which is a huge amount of potentially healthy lung tissue,” Dr. Liao said. “Our goal is to use the simultaneous integrated boost to maintain the standard dose to the margin and maximize the dose to the tumor.” Previous efforts to increase the dose to the tumor by adding extra treatment fractions have led to increased toxicity to nearby tissue.

In IMPT, the simultaneous integrated boost is delivered using pencil beam scanning. The radiation oncologist “paints” protons in multiple layers in both the tumor and the margin. Each layer of protons delivered to the tumor has a higher dose than that delivered to the margin. For IMRT, the simultaneous integrated boost technique is more like film exposure, with the tumor being exposed to photon radiation longer than the margin is.

In the trial, IMRT and IMPT with simultaneous integrated boost are delivered 5 days per week for 6 weeks (30 fractions). The phase I portion of the trial determined the total doses for the phase II portion: 60 Gy for healthy tissue in the tumor margin and up to 78 Gy for tumor tissue.

The phase II portion of the trial is still accruing patients. The goals of this portion are to assess local tumor control and toxic effects in patients treated with the new simultaneous integrated boost and to determine whether simultaneous integrated boost with IMPT or IMRT more effectively controls the tumor.

Candidates for this trial include patients with stage II or III NSCLC whose tumors are difficult to excise (such as pulmonary sulcus tumors), those for whom induction chemotherapy failed, or those who underwent surgery but experienced tumor recurrence. “These advances in radiation therapy have exciting applications for NSCLC,” Dr. Liao said. “These ground-breaking trials will offer new hope for these patients.”

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—Dr. Quynh-Nhu Nguyen

“This could be a practice-changing trial.”

—Dr. Zhongxing Liao

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To learn more about ongoing clinical trials at MD Anderson, visit www.clinicaltrials.org.

FURTHER READING
By Joe Munch

A groundbreaking clinical trial is demonstrating the promise of BRAF inhibition in multiple types of cancer and helping change the way researchers test treatments for cancers with actionable genetic aberrations.

About 15% of cancers have BRAF mutations, and approximately 70%–90% of these are BRAF V600 point mutations. BRAF V600 mutations, which were first discovered and successfully targeted therapeutically in melanoma, have also been reported in non–small cell lung cancer (NSCLC), colorectal cancer, cholangiocarcinoma, papillary thyroid cancer, multiple myeloma, and hairy cell leukemia. Now, in one of the first multicenter trials enrolling patients on the basis of their genetic aberration status rather than tumor type, investigators are finding that BRAF V600 mutations in many cancers can be targeted with the BRAF inhibitor vemurafenib, which is already approved for the treatment of advanced melanoma.

“We wanted to know how to go after this gene mutation in other cancers like we did in melanoma,” said Vivek Subbiah, M.D., an assistant professor in the Department of Investigational Cancer Therapeutics and The University of Texas MD Anderson Cancer Center's principal investigator for the trial. “If we see promising signals of activity in these tumor types, they could be definitively explored in another study.”

A “basket” study design

Traditional clinical trials enroll cancer patients on the basis of their tumors’ site of origin and histologic subtype. This approach presents a bit of a problem when investigating BRAF inhibitors. BRAF aberrations occur in about half of melanomas and virtually all hairy cell leukemias, but they are otherwise rare, even among common cancers, making it exceedingly difficult to recruit sufficient numbers of patients for clinical trials.

The answer, Dr. Subbiah and his colleagues found, is to use a “basket” study design, which allows investigators to assess, in a single study, groups of patients with many different tumor types for therapy response. Study arms with high response rates can be expanded to include more patients, and arms with low response rates can be eliminated, enabling investigators to zero in on the populations that would most benefit from the drug.

“In a basket study, you can include multiple cancer types as opposed to designing 15 different trials.”

– Dr. Vivek Subbiah

Early results show promise

The phase II trial, whose preliminary results for 122 patients were published last August in the New England Journal of Medicine, enrolled patients with BRAF V600–positive cancer in cohorts according to cancer type: NSCLC, ovarian cancer, colorectal cancer, cholangiocarcinoma, breast cancer, multiple myeloma, and all others. Vemurafenib was found to be espe-
“It’s important that we learn not only which cancers respond to BRAF inhibitor therapy but also which cancers don’t respond.”

– Dr. Vivek Subbiah

chially effective in two of these groups. Among 19 NSCLC patients, eight (42%) had a complete or partial response to vemurafenib, and the median progression-free survival duration was 7.3 months. And among 14 patients with either Erdheim-Chester disease or Langerhans cell histiocytosis (two rare dendritic cell disorders), six (43%) had a complete or partial response. Furthermore, none of these 14 patients had disease progression during therapy, the median duration of which was 5.9 months.

“What we’ve seen in the trial has been interesting,” Dr. Subbiah said. “We’ve learned that common diseases like lung cancer and even rare diseases like Langerhans cell histiocytosis can be treated with vemurafenib if they have BRAF aberrations.”

The researchers also found that colorectal cancer was not treatable with vemurafenib alone (citing no responses in 10 patients) but was treatable with vemurafenib plus cetuximab, an epidermal growth factor receptor (EGFR) inhibitor. With the MAPK and EGFR signaling pathways blocked by vemurafenib and cetuximab, respectively, about half of the 27 patients with aggressive BRAF V600–positive colorectal cancer had some tumor regression (though not a complete or partial response), and one patient had sufficient regression to meet the criteria for a partial response. These findings underscore the biological aggressiveness and treatment-resistant nature of BRAF V600–positive colorectal cancer.

“It’s important that we learn not only which cancers respond to BRAF inhibitor therapy but also which cancers don’t respond; and if they don’t respond, we need to learn why they don’t respond,” Dr. Subbiah said.

In addition, two of seven patients with anaplastic thyroid cancer had a complete or partial response. “Anaplastic thyroid cancer is one of the toughest diseases known to humankind,” Dr. Subbiah said. “These patients typically don’t live beyond 6 months. But a subset of patients with anaplastic thyroid cancer have the BRAF V600 mutation, and some of these patients responded to BRAF inhibitor therapy in our study. And this gives us the motivation to go after this target in other patients with this disease.”

FOR MORE INFORMATION
Dr. Vivek Subbiah .......... 713-563-0393

FURTHER READING

CLINICAL TRIALS: Basket Trials

Several ongoing trials at MD Anderson use the basket design to enroll patients based on their tumors’ molecular characteristics. Some of these trials are listed below.

A phase II, open-label study in subjects with BRAF V600E–mutated rare cancers with several histologies to investigate the clinical efficacy and safety of the combination therapy of dabrafenib and trametinib (2013-0918). Principal investigator (PI): Dr. Vivek Subbiah. The main goal of this study is to determine the overall response rate to dabrafenib–trametinib combination therapy in patients with rare BRAF V600E–mutated solid tumors or hematologic malignancies.

Modular phase II study to link targeted therapy to patients with pathway-activated tumors: Module 7—Ceritinib (LDK378) for patients whose tumors have aberrations in ALK or ROS1 (2014-0669). PI: Dr. Subbiah. The goals of this study are to assess the clinical benefit associated with ceritinib treatment and the relationship between ALK or ROS1 pathway status and response to treatment with ceritinib.

MY Pathway: An open-label phase IIA study evaluating trastuzumab/ pertuzumab, erlotinib, vemurafenib, and vismodegib in patients who have advanced solid tumors with mutations or gene expression abnormalities predictive of response to one of these agents (2014-0459). PI: Dr. Funda Meric-Bernstam. The goal of this study is to evaluate the efficacy of trastuzumab plus pertuzumab, erlotinib, vemurafenib, and vismodegib in patients who have advanced solid tumors with molecular alterations predictive of response to one or more of these agents and for whom other therapies are not available or are not suitable options.

FOR MORE INFORMATION
Reducing the Likelihood of Second Primary Cancers in Cancer Survivors

By Kathryn Hale

Cancer survivors are at risk of not only cancer recurrence but also a second primary cancer. Their risk of a second cancer is typically higher than the risk of a first cancer in the general population, but an individual survivor’s risk varies by the type of initial cancer and other factors. To help cancer survivors manage this risk, the clinical services at The University of Texas MD Anderson Cancer Center include risk reduction and screening for second primary cancers.

The unprecedented growth in the number of cancer survivors—according to the American Cancer Society, this population grew from 13.7 million to 14.5 million between 2012 and 2014—has created a demand for health care services tailored to these patients’ needs.

“Cancer survivors have unique medical and psychosocial needs,” said Therese Bevers, M.D., a professor in the Department of Clinical Cancer Prevention and the medical director of both the Cancer Prevention Center and the Prevention Outreach Program at MD Anderson, “and these needs have not always been adequately addressed. But that is changing.”

MD Anderson is looking at every possible way to improve survivors’ health and quality of life, and one of those ways, Dr. Bevers said, is reducing their risk of getting another cancer. For this reason, in addition to 11 multidisciplinary, disease-specific adult cancer survivorship clinics and one childhood cancer survivorship clinic, the institution offers risk reduction and cancer screening services to cancer survivors through the Cancer Prevention Center.

Reducing survivors’ risk of a second cancer

At MD Anderson, the comprehensive survivorship care plan for all patients comprises four domains: surveillance for recurrence of the cancer; monitoring and treatment for late effects of the cancer or its treatment; optimization of psychosocial functioning, which focuses on quality of life issues; and prevention, which aims to reduce the risk of second primary cancers and also screen for the early detection of such cancers. It is this last domain that is overseen by Dr. Bevers.

Dr. Bevers and the Cancer Prevention Center staff identify each survivor’s risk factors and make recommendations through a two-pronged approach of risk reduction and screening. Risk reduction looks at strategies for reducing or eliminating risk factors to prevent cancers from developing, while screening focuses on early detection, whether of a precancerous lesion that can be removed before it progresses to cancer or an early-stage cancer that is much more likely to be treated successfully than a late-stage cancer.

While not all survivorship care at MD Anderson is provided through the Cancer Prevention Center, more and more patients benefit from the center’s focus on reducing the risk of a second primary cancer.

Risk factors for a second primary cancer are not much different than those for an initial cancer. Some of these factors cannot be controlled, such as genetics and aging; others are difficult to control, such as environmental exposures; but some can be controlled, such as lifestyle factors and preventable infections. And there are factors unique to cancer patients, generally related to previous cancer treatment, that increase the risk of certain cancers. For example, radiation therapy can increase the risk of skin cancer, and some chemotherapy agents can increase the risk of leukemia.

While little can be done to mitigate the unavoidable risk factors, many strategies can be employed to eliminate avoidable risk factors. Lifestyle factors such as diet, body weight, physical activity, sun and other ultraviolet light exposure, alcohol use, and tobacco use affect the risk of a second primary can-

“Our biggest opportunity for prevention is education, particularly about healthy lifestyle and its power to reduce cancer risk.”

– Dr. Therese Bevers

www.mdanderson.org/oncolog 5
Reducing the Likelihood of Second Primary Cancers

[Continued from page 5]

cancer for cancer survivors. Infections such as human papillomavirus and hepatitis B are cancer risk factors that can be prevented through vaccination.

While current thinking is that about half of all cancers in the general population are preventable through healthy lifestyle choices and vaccinations, Dr. Bevers believes that number may be closer to 70% if all factors are considered. She acknowledges that the percentage of preventable cancers may be a little lower for cancer survivors because of their inherently higher risk and the unavoidable risk factors related to their cancer treatment, but the Cancer Prevention Center’s mission for cancer survivors is built on the principle that a substantial number of second primary cancers can be prevented.

Healthy Living Clinic helps survivors reduce risk

To help cancer survivors improve their overall health and reduce specific lifestyle-related cancer risks, the Cancer Prevention Center launched the Healthy Living Clinic in January 2013. Clinic staff provide one-on-one counseling targeted at reducing lifestyle-related risks through behavioral changes in five areas: nutrition (including weight management), physical activity, tobacco cessation, psychosocial needs, and complementary therapies. The staff help survivors set specific goals and provide regular follow-up, in person or by phone or computer, to help the survivors meet their goals. Patients may be referred to MD Anderson’s successful Tobacco Treatment Program or to a registered dietitian, social work counselor, or health educator if needed.

To help educate patients about reducing lifestyle-related risks, the Healthy Living Clinic works with the Office of Cancer Survivorship, which has produced booklets and videos to help survivors and their families learn about the specifics of recommended lifestyle changes.

“Our biggest opportunity for prevention is education, particularly about healthy lifestyle and its power to reduce cancer risk,” Dr. Bevers said. “As patients transition to cancer survivorship, their focus shifts from disease to health and wellness. At that point, they are extremely motivated to adopt changes that help promote wellness and reduce further cancer risk. They are ready to hear about avoidable risks and how reducing or eliminating those risks can help prevent second cancers. They’re listening, and that’s when we start the education process.”

Continuing Care After Cancer

Reducing the risk of a second primary cancer is only one aspect of comprehensive care for cancer survivors, and such care requires a partnership between cancer specialists and community physicians. Patients who complete their cancer treatment at MD Anderson typically transition gradually back to their primary care provider, continuing to receive survivorship care at MD Anderson while receiving other primary and specialty care in their community. “Our goal is to eventually return patients to their community clinicians for all their medical needs,” Dr. Bevers said. “Our survivorship program is about partnering with primary care clinicians in the community. We want them to learn about the special risks and challenges faced by cancer survivors and to join with us in addressing those challenges.”

To help community clinicians learn about comprehensive survivor care, MD Anderson has published its clinical practice algorithms to guide the care of survivors of different types of cancer. Each algorithm is regularly updated and includes guidelines and recommendations for the four domains of care: surveillance for recurrence, monitoring for late effects, psychosocial care, and prevention of second primary cancers.

Clinicians in the community are invited to review the survivorship algorithms at http://bit.ly/1Vses2J. Other resources for patients and clinicians are available through the Office of Cancer Survivorship, which can be reached by email at survivorship@mdanderson.org.

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The Growing Number of Cancer Survivors: About 65% of patients diagnosed with any type of cancer 5 years ago are still alive, and that percentage is substantially higher for some cancer types, including two of the four most common cancers in the United States. Specifically, the American Cancer Society reported that in 2014 the 5-year relative survival rates were 99% for patients with prostate cancer, 89% for those with breast cancer, and 65% for those with colon cancer. However, the rate for patients with lung cancer remained among the lowest for all cancers at 17%.
Three-dimensional conformal radiation therapy (3D-CRT) uses multiple devices called collimators to shape radiation beams so that they resemble the shape of the tumor. The beams are delivered from multiple directions, and their shape helps reduce the damage to healthy tissue.

Intensity-modulated radiation therapy (IMRT) is similar to 3D-CRT, but in IMRT the collimators adjust the intensity of the beams as well as their shape. Adjusting the intensity of the beams reduces the radiation dose to nearby healthy tissue while increasing the dose to the tumor or specific parts of it.

Image-guided radiation therapy uses repeated imaging scans (such as CT, MRI, or PET) during treatment to determine if the patient or radiation beams need to be repositioned during treatment in response to movement of the tumor. This technique is often used together with other types of EBRT.

Proton therapy uses proton beams to kill cancer cells. Protons deliver the bulk of their energy at the end of their path, with little energy deposited in tissue along the way. Whereas photons may deliver a substantial radiation dose to the healthy tissue they pass through on the way to the tumor, protons deliver most of the radiation dose directly to the tumor.

Stereotactic radiosurgery is often used to give a large dose of radiation to a small tumor area from multiple angles in a single session. This method is used only to treat small tumors with well-defined edges, such as those found in the brain and spinal cord.

Internal radiation therapy
Internal radiation therapy, or brachytherapy, uses radioactive sources sealed in “seeds” that are placed in the body through a needle or catheter. The radioactive seeds may be placed near a tumor or in a surgical cavity (the space left when a tumor is removed).

In high-dose-rate brachytherapy, a highly radioactive source is placed in the body for a few minutes and then removed. In low-dose-rate brachytherapy, temporary or permanent radioactive seeds are placed in the body to continuously give off radiation for days, weeks, or months as the radioactive source decays.

Systemic radiation therapy
In systemic radiation therapy, radioactive drugs called radiopharmaceuticals are given to patients through injection or by mouth. The radioactive substance sometimes is bound to a specially designed antibody (a monoclonal antibody) that seeks out and attaches to cancer cells, delivering radiation to the tumor site.

Radiation and other treatments
Radiation therapy may be used on its own or combined with other cancer treatments. Radiation is often given before surgery to shrink the tumor or given during or after surgery to kill off remaining cancer cells. Combining chemotherapy with radiation therapy (chemoradiation) is also now a standard treatment for many cancers. The drugs given often make the tumor more sensitive to radiation.

Whether used alone or with other cancer treatments, the techniques described above have made radiation therapy safer and more effective than ever before.

B. Strubberg

For more information:
- Ask your physician
- Visit www.mdanderson.org
- Call askMDAnderson at 877-632-6789
Breast Cancer Survivorship Course

The Breast Cancer Survivorship Course is one of several continuing medical education (CME) programs offered by The University of Texas MD Anderson Cancer Center’s Professional Oncology Education program. The goal of the course is to help equip health care professionals to care for the growing number of breast cancer survivors.

The Breast Cancer Survivorship Course, which was recently updated, comprises 21 lessons on topics related to the unique challenges faced by breast cancer survivors and strategies for the appropriate long-term follow-up care of these patients. Each lesson includes a lecture by an MD Anderson physician, advanced practice nurse, or pharmacist followed by a brief quiz.

In addition to overviews of breast cancer epidemiology, etiology, diagnosis, pathology, and treatment, the lessons provide insight into recognizing and managing late effects of surgery, radiation therapy, endocrine therapy, and chemotherapy. One lesson addresses issues related to breast reconstruction; other topics in the course include common sites of metastasis, surveillance and risk reduction for second primary cancers in the breast or other parts of the body, and identifying patients for whom genetic testing is appropriate. Most of the lessons are 15–40 minutes long.

The entire Breast Cancer Survivorship Course is available online at no cost at http://bit.ly/1TAdFpM. Physicians and other health care professionals can sign in to take the course for CME credit, and anyone can view individual lectures without signing in.

“Useful Resources” introduces tools for community physicians and other medical professionals available free of charge on MD Anderson’s Web site.

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