Laser Interstitial Thermal Therapy for Spinal Metastases

Laser technique may be alternative to open surgery prior to stereotactic radiation therapy for metastases adjacent to the spinal cord

By Joe Munch

In many patients with spinal metastases, stereotactic radiation therapy can provide effective local tumor control to prevent spinal cord compression and subsequent paralysis. However, in patients in whom a metastasis is touching or displacing the spinal cord, the tumor must be separated from the spinal cord before stereotactic radiation can be safely delivered. Until recently, this meant that such patients would have to endure an open surgery, along with its attendant potential complications and delays in other oncological treatment. But now a surgeon at The University of Texas MD Anderson Cancer Center is adapting an existing ablation method as an alternative to surgery to treat spinal metastases in select patients.

To avoid the risks associated with surgery for spinal metastases, Claudio Tatsui, M.D., an associate professor in the Department of Neurosurgery, has adapted a laser-based thermal ablative technique routinely used to treat tumors in the brain, prostate, liver, and other sites. The resulting procedure, spinal laser interstitial thermal therapy (SLITT), is currently performed only at MD Anderson.

Instead of having to surgically remove the portion of the tumor adjacent to the dura mater prior to stereotactic radiation therapy, Dr. Tatsui said, “We’re using a laser to heat and destroy the tumor in the epidural space and then covering the residual disease with stereotactic radiation therapy.”

During spinal laser interstitial thermal therapy, magnetic resonance imaging thermometry shows the real-time temperature at the preset monitoring point and safety stops (orange and green boxes, respectively, in degrees Celsius) around the laser probe, allowing the surgeon to ensure that the laser heats the tumor tissue, but not nearby vital structures, to a temperature that causes irreversible damage. (The red and yellow area is a heat artifact caused by the patient’s heartbeat, not the laser.) Image courtesy of Dr. Claudio Tatsui.
Performing the procedure

In SLITT, a Jamshidi bone marrow needle is advanced into the spinal metastasis under magnetic resonance imaging (MRI)– or computed tomography–based guidance. The needle’s central trocar is removed, and a Kirschner wire is inserted through the needle. The Jamshidi needle is then removed, leaving the Kirschner wire to serve as a guide for placing an access cannula. Additional cannulas are usually placed; the number used depends on the size and location of the tumor.

For the ablation step, a laser probe is advanced to the end of the access cannula in the tumor, and the cannula is retracted slightly to expose the tip of the laser probe. The probe is then energized to heat the surrounding tissue to a temperature that irreversibly damages tumor cells (typically 50–74°C); the temperature at the interface between the tumor and vital structures is maintained at less than 50°C to avoid damaging those structures. The heating process is monitored in real time with MRI thermometry.

“What makes this procedure special is not the temperature itself, but the monitoring of the temperature in space,” Dr. Tatsui said. “The MRI lets me localize the temperature and treat lesions near vital organs without damaging those structures. We can find in real time where the heat is being applied, the extent of the damage, and if there is a need for additional laser probes.”

The heating process is repeated several times to ensure adequate thermal coverage of the tumor. The laser probe can deliver tumor-killing temperatures within a radius of 5–7 mm; and typically three access cannulas are needed per spinal lesion, although Dr. Tatsui said that he has used as many as eight cannulas for very large tumors. Preparing each cannula takes about 1 hour, but the ablation procedure itself takes only 3 or 4 minutes, depending on the complexity of the case. The procedure can be repeated as many times as needed if the tumor grows back.

As with traditional open surgery, SLITT is followed by stereotactic radiation therapy. But SLITT enables a much quicker return to treatment than does surgery. Whereas the median hospital stay following surgery is 7 days, that following SLITT is only 2 days, Dr. Tatsui said, noting that the procedure can also benefit patients for whom a long interruption in systemic treatment is not ideal.

Another benefit of SLITT is that it appears to be substantially less painful than open surgery. “We’ve looked at patients’ self-reported pain scores before and after the procedure, and we haven’t seen the immediate increase in pain that we see with standard open surgery,” Dr. Tatsui said.

Selecting the right patients

Dr. Tatsui has used SLITT followed by stereotactic radiation to treat epidural spinal metastases from melanoma and from breast, lung, prostate, and other cancers but has most often used it in patients with metastases from renal cell carcinoma, which is notoriously resistant to chemotherapy and conventionally fractionated radiation therapy. “We’re using this technique to treat pretty much any metastatic tumor in the epidural space that is resistant to conventional radiation therapy,” he said.

The procedure has the most benefit in patients with metastatic tumors in the thoracic spine, where about 70% of spinal metastases occur. Dr. Tatsui said he tries to avoid performing SLITT in patients with metastases in the lumbar spine because these tumors can involve or abut motor nerves, which are very sensitive to heat.

“I’ve had two cases where the tumor was near a motor nerve and the patients had dysfunction of the nerve after SLITT,” Dr. Tatsui said. “So we
tend to do the procedure where there are only sensory nerves. The thoracic spine, from T2 to T12, is where we get the best results with this technique.”

SLITT has also been used without stereotactic radiation in eight patients, Dr. Tatsui said. These patients had already received the maximum cumulative dose of radiation to the spine and were not strong candidates for palliative surgery because of the scarring from radiation and the associated poor healing. The results were promising, Dr. Tatsui said, and if the tumors recur, SLITT can be repeated.

Although SLITT could be used to treat primary tumors in the spine, Dr. Tatsui said, such tumors are probably more effectively treated with appropriate oncological (i.e., radical) resection.

Looking forward
Dr. Tatsui said that he and his colleagues have been very pleased with what they've observed in combining SLITT with stereotactic radiation therapy, and a pilot study (No. 2015-0481) evaluating the safety and accuracy of intraoperative MRI guidance for SLITT is ongoing. Now, he said, “We’re retrospectively comparing outcomes of our laser ablation protocol with those of open surgery, and we’re observing very positive results. We plan a future prospective study to directly compare SLITT and open surgery in the management of spinal metastasis.

“I envision that this will be an alternative to open surgery, especially for patients with aggressive systemic disease or significant comorbidities that preclude surgery,” Dr. Tatsui said.

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FURTHER READING

Immunotherapy Plus Targeted Therapy for Anaplastic Thyroid Cancer

Trial combines atezolizumab with targeted or cytotoxic agents for patients with anaplastic or poorly differentiated thyroid cancer

By Bryan Tutt

Most patients with anaplastic thyroid cancer present with locally invasive or distant metastatic disease, making potentially curative resection impossible. Chemoradiation and especially targeted therapies can slow the cancer's progression, but responses are often cut short as the disease mutates and develops resistance; most patients die within 1 year. In hopes of prolonging responses and extending survival for patients with anaplastic thyroid cancer, a new clinical trial is adding immunotherapy to targeted therapy and cytotoxic chemotherapy regimens.

Historically, recruiting patients with anaplastic thyroid cancer for clinical trials has been difficult, in part because such patients tend to have poor performance status or comorbidities that exclude them from trials. “Most patients with anaplastic thyroid cancer aren’t eligible for clinical trials,” said Maria Cabanillas, M.D., an associate professor in the Department of Endocrine Neoplasia and Hormonal Disorders at The University of Texas MD Anderson Cancer Center.

Dr. Cabanillas and her colleagues designed a clinical trial that includes patients who have challenges associated with advanced anaplastic thyroid cancer. “We want to be able to treat the kind of patient that’s really out there,” she said. “We want the results to be applicable across the anaplastic thyroid cancer patient population.”

The clinical trial (No. 2016-0916) combines the immunotherapy drug atezolizumab with cytotoxic chemotherapy or one of three targeted therapy regimens for patients with unresectable or metastatic anaplastic thyroid cancer. The addition of immunotherapy, the researchers believe, will overcome some of the limitations of these treatments given alone.

Limitations of existing treatment
Patients with unresectable anaplastic thyroid cancer typically receive radiation with radiosensitizing chemotherapy. Chemoradiation can slow tumor growth, but radiation is not always a safe option and fails to address the metastatic disease present in 50% of patients at diagnosis.

The most common driver mutations for anaplastic thyroid cancer occur in the BRAF or RAS genes, and drugs that target the BRAF kinase have had higher response rates than cytotoxic chemotherapy. Drugs that target MEK (which shares a signaling pathway with BRAF and RAS) or VEGF (vascular...
A New Era in Follicular Lymphoma

Newly approved drugs, clinical trials represent shift from cytotoxic to targeted and immunotherapeutic agents

By Bryan Tutt

Although follicular lymphoma remains incurable, recently approved targeted and immunotherapeutic agents have extended remissions and overall survival durations for patients. As phase III trials of even more new treatment combinations approach completion, knowledge of the available treatment options can help physicians recommend the most appropriate treatment for their patients with newly diagnosed or relapsed or refractory follicular lymphoma.

For nearly 40 years, cytotoxic chemotherapy was the standard of care for follicular lymphoma, which is the second most common non-Hodgkin lymphoma and the most common indolent lymphoma. The standard of care began to change with the U.S. Food and Drug Administration (FDA)’s approval of the anti-CD20 antibody rituximab for relapsed/refractory follicular lymphoma in 1997 and for first-line treatment of follicular lymphoma in 2006. Since then, more novel agents have emerged to treat follicular lymphoma.

“We’ve seen a paradigm shift in the past 5 years, with most new treatment regimens incorporating novel targeted or immunotherapeutic agents,” said Nathan Fowler, M.D., an associate professor in the Department of Lymphoma and Myeloma at The University of Texas MD Anderson Cancer Center.

The changing standard of care

The standard first-line therapies for follicular lymphoma are rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP); and rituximab and bendamustine. In most patients, these rituximab-containing regimens achieve remissions lasting 4–7 years. Rituximab is used alone as a first-line treatment for patients whose frailty or comorbidities preclude cytotoxic therapy. Single-agent rituximab also may be beneficial as maintenance therapy for patients who experience a partial remission with any first-line regimen.

Second-line treatments for follicular lymphoma include re-exposure to common first-line regimens, the radiopharmaceutical yttrium Y 90–ibritumomab tiuxetan, and the recently approved combination of bendamustine and obinutuzumab, a second-generation anti-CD20 antibody.

The choice of third-line treatment for relapsed/refractory follicular lymphoma depends largely on a patient’s age, how long the most recent remission lasted, and how aggressive the disease is. In 2014, monotherapy with the PI3K inhibitor idelalisib was approved for treating patients with follicular and small lymphocytic lymphomas who have received at least two previous lines of therapy. Dr. Fowler, who led phase I and II trials of idelalisib, said the drug is only one of several third-line options. “If the second line of therapy fails, we often encourage participation in a clinical trial of a novel agent or referral to our stem cell transplant center,” he said. Patients also may be eligible to participate in clinical trials of T cells or natural killer cells expressing chimeric antigen receptors (see “Chimeric Antigen Receptor–Directed Natural Killer Cells for B Cell Malignancies,” OncoLog, May/Jun 2017).

As a result of the shifting standard of care, outcomes have improved for patients with follicular lymphoma. Dr. Fowler said, “Several long-term follow-up studies of patients who have received current standard therapies have shown that, unlike patients 10–15 years ago, most patients today will not die of their disease.”

More changes to come

The standard of care for follicular lymphoma continues to evolve. Several multicenter phase III randomized controlled trials comparing new treatment regimens with standard therapies are ongoing or recently completed (see table, p. 5), and Dr. Fowler expects some of these new regimens to be approved by the FDA within the next few years.

The combination of rituximab and the immune modulator lenalidomide, a regimen commonly known as R2, is in phase III trials for patients with previously untreated (No. 2011-0805) or...
relapsed/refractory (2015-0038) follicular lymphoma. Dr. Fowler said that earlier trials of this treatment combination also were performed at MD Anderson (see graphs, p. 4). “We were the first center to do combination immunotherapy trials of a monoclonal antibody with an immune modulator in patients with untreated follicular lymphoma,” he said. Both phase III trials of R² have completed enrollment, and Dr. Fowler expects to see preliminary results in the coming months.

A phase III trial of obinutuzumab and cytotoxic chemotherapy in patients with previously untreated follicular lymphoma also recently completed enrollment. Dr. Fowler—who was MD Anderson’s principal investigator of the phase III trial that led to the FDA’s approval of obinutuzumab and bendamustine as a second-line therapy—anticipates the combination’s approval as a first-line therapy.

Two ongoing phase III trials are evaluating the Bruton tyrosine kinase inhibitor ibrutinib (which is approved for the treatment of other indolent lymphomas) for patients with follicular lymphoma. In one trial (No. 2014-0088), ibrutinib is given with R-CHOP or with rituximab and bendamustine to patients with relapsed/refractory disease. This trial has completed enrollment. In the other trial, ibrutinib is given with rituximab to previously untreated follicular lymphoma patients in whom cytotoxic therapy is contraindicated. Dr. Fowler, the ibrutinib-rituximab trial’s national principal investigator, said the trial will soon begin enrolling patients at MD Anderson. Patients in the ibrutinib-rituximab trial must be at least 70 years old or at least 60 years old with one or more major comorbidities, and it is hoped that the noncytotoxic regimen will yield a better progression-free survival rate than monotherapy with rituximab.

Noncytotoxic regimens are of increasing interest in follicular lymphoma research. “In a disease where patients are surviving longer,” Dr. Fowler said, “we have to pay a lot more attention to the short- and long-term toxic effects of any given therapy because patients are going to have to live with this disease along with any side effects of the treatment.”

Therefore, Dr. Fowler said, “We’ve recently launched an initiative to open studies focusing on immunotherapy for follicular lymphoma.”

One current trial at MD Anderson (No. 2015-1063) is evaluating the PD-L1 (programmed cell death protein 1 ligand) inhibitor durvalumab alone or combined with other follicular lymphoma treatments. Another trial (No. 2015-0361), led by Loretta Nastoupil, M.D., an assistant professor in the Department of Lymphoma and Myeloma, is testing the efficacy of R² plus ibrutinib. And a third trial (No. 2013-0261) is assessing the safety and tolerability of obinutuzumab given with lenalidomide. These and other trials of immunotherapeutic and targeted agents for patients with follicular lymphoma will be discussed in detail in an upcoming issue of OncoLog.

“The field of follicular lymphoma treatment is changing, and outcomes are improving,” Dr. Fowler said. “And with the new tools we are discovering, I’m optimistic that the future outcomes of patients diagnosed with this chronic disease will continue to improve.”

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For more information about ongoing clinical trials for patients with follicular lymphoma, visit www.clinicaltrials.org.
Anaplastic Thyroid Cancer

[Continued from page 3]

endothelial growth factor) also have shown promise against the disease. However, as with cytotoxic chemotherapy, the responses to such targeted drugs are limited by the emergence of resistance mutations, which lead to disease progression.

Immunotherapy could potentially be used against anaplastic thyroid cancer, as preclinical studies have shown that anaplastic thyroid tumors express high levels of the immune checkpoint protein PD-1 (programmed cell death protein 1) and its ligand, PD-L1. However, it takes time for the immune system to respond to drugs that inhibit PD-1 and PD-L1, and time is a luxury that anaplastic thyroid cancer patients do not have.

“In patients with other types of cancer, immunotherapy usually takes two or three cycles before we see a response,” Dr. Cabanillas said. “But patients with anaplastic thyroid cancer can’t wait that long because their disease is just so aggressive. Their condition would deteriorate, and they might die before we could get a response.” Immunotherapy, therefore, may be most effective given alongside drugs that are known to slow tumor growth.

Clinical trial

The clinical trial of the PD-L1 inhibitor atezolizumab plus targeted or cytotoxic therapy, patients with advanced anaplastic or poorly differentiated thyroid cancer begin treatment with standard or nanoparticle albumin–bound paclitaxel. When molecular test results arrive, patients are assigned to one of three targeted therapy cohorts. In each targeted therapy cohort, patients are screened for contraindications to the targeted drugs and assigned to another cohort if necessary. Image courtesy of Dr. Maria Cabanillas.

Once the molecular test results arrive, patients are assigned to treatment cohorts on the basis of their genetic mutations (see schema, this page). Patients with BRAF mutations are assigned to cohort 1 and receive the BRAF inhibitor vemurafenib, the MEK inhibitor cobimetinib, and the immunotherapy drug atezolizumab. Patients with RAS mutations are assigned to cohort 2 and receive cobimetinib and atezolizumab. Patients with neither mutation are assigned to cohort 3 and receive the VEGF inhibitor bevacizumab and atezolizumab. Patients who are ineligible for any of these 3 cohorts are assigned to cohort 4 and treated with standard or nanoparticle albumin–bound paclitaxel and atezolizumab. Patients may receive radiation therapy if needed; this is decided on a case-by-case basis.

Patients with risk factors or comorbidities that preclude treatment with a drug used in one cohort are assigned to another cohort. “We want to match both the tumor and the appropriate medical condition,” Dr. Cabanillas said.

“We don’t want to treat a patient with a drug that might worsen a medical problem.”

Despite the rarity of both anaplastic and poorly differentiated thyroid cancers, Dr. Cabanillas believes that the trial will be able to complete its planned enrollment of 50 patients, at least 36 of whom must have anaplastic thyroid cancer. “We designed the atezolizumab trial to be available to about 90% of the new anaplastic thyroid cancer patients we see,” she said. She added that MD Anderson’s Anaplastic Thyroid Cancer Clinic has a multidisciplinary program—Facilitating Anaplastic Thyroid Cancer Specialized Treatment, or FAST—that expedites the evaluation of patients with the disease and helps enroll them in clinical trials if appropriate (see “Anaplastic Thyroid Cancer,” OncoLog, April 2016).

Dr. Cabanillas emphasized the need for immediate referral of patients with suspected anaplastic thyroid cancer to a large cancer center. “If patients are referred early, we can probably get them into a clinical trial of a targeted agent plus immunotherapy,” she said. “We feel like that is the best treatment strategy for anaplastic thyroid cancer.”

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For more information about the clinical trial of immunotherapy plus targeted or cytotoxic therapy for patients with anaplastic or poorly differentiated thyroid cancer, visit www.clinicaltrials.org and search for study No. 2016-0916.

For more information about MD Anderson’s Anaplastic Thyroid Cancer Clinic, visit http://bit.ly/1RO2pL.
Understanding Clinical Trials

Trials provide access to new cancer treatments

New cancer treatments typically undergo years of testing before they are approved for standard use in people. The last steps in this testing process are clinical trials, which study how new treatments work in patients.

Cancer clinical trials take place in up to four phases. Each phase asks different questions and gathers data to support further research. The phase indicates how much research has been done and approximately how many people participate in the study.

**Phase I trials**

Phase I trials usually test a new treatment in humans for the first time, after the treatment has been shown to be safe and effective in laboratory and animal studies. A phase I trial can also be used to evaluate an approved drug at higher doses or in a different disease. Fifteen to 30 people usually participate, and patients with different types of cancer might be allowed to enter the trial. These patients have usually tried other treatments without success.

In phase I trials, researchers focus on the safety of the treatment, studying the best way to administer the new treatment, the maximum safe dose, and how often the treatment should be given. One benefit of participating in a phase I trial is being among the first to receive a new treatment that might prove effective against cancer. However, phase I trials also carry risks, since the effectiveness of the treatment in people has not been demonstrated and no one yet knows what side effects might occur.

**Phase II trials**

If the new treatment is shown to be safe in a phase I trial, the study progresses to phase II. In phase II trials, researchers continue to test the safety of a new treatment and begin to evaluate how well it works. These trials typically enroll fewer than 100 participants, and eligibility is usually based on which prior treatment(s) participants have received. Recruiting enough participants for a phase II trial may take up to 2 years.

**Phase III trials**

Treatments that are shown to be effective in phase II trials are further refined and studied in phase III trials. A phase III trial usually determines whether a treatment will be approved for a particular disease and typically enrolls between 100 and several thousand people. These participants are divided into two or more study groups, depending on the research questions being asked.

In phase III trials, researchers try to find out whether the new treatment works better than, the same as, or worse than the standard treatment. Even though only about half the patients in a phase III trial will get the new treatment, those who don’t will receive the standard treatment, which has so far proved to be the best available. Despite a popular misconception, placebos (fake drugs) are rarely used in cancer treatment trials. If a placebo is used, it is given along with the standard treatment.

Risks of participating in a phase III trial can include adverse effects that were not noted in prior studies or are worse than those found in standard treatment. It is also possible that the new therapy will be less effective than the standard treatment. Recruitment for phase III trials can take 3–4 years.

**Phase IV trials**

Phase IV trials are rare. They are conducted after a new treatment has been approved for standard use and are used to measure the long-term safety and effectiveness of the treatment.

**Patient participation**

After receiving a thorough explanation of the possible risks and benefits of the treatment being studied, patients can decide whether to participate in a clinical trial. Patients who choose to take part in clinical trials may or may not receive a benefit beyond what they would have received with standard care, but their participation will add to what is known about their disease and perhaps lead to a cure.

**FOR MORE INFORMATION**

- Ask your physician
- Visit www.clinicaltrials.org
- Call askMDAnderson at 877-632-6789
Repeat Surgery for Close Margins May Be Unnecessary for DCIS Patients Receiving Radiation Therapy

Patients with ductal carcinoma in situ (DCIS) who have breast-conserving surgery that results in narrow, or “close,” negative surgical margins may not have to undergo repeat surgery if radiation therapy is performed, according to a recent analysis by researchers at The University of Texas MD Anderson Cancer Center.

The retrospective study—led by Audree Tadros, M.D., and Henry Kuerer, M.D., Ph.D., a fellow and a professor, respectively, in the Department of Breast Surgical Oncology—was performed to clarify the benefits of radiation therapy in preventing locoregional recurrence in DCIS patients after breast-conserving surgery with negative surgical margins less than 2 mm (i.e., with less than 2 mm of tumor-free tissue surrounding the tumor in the excised specimen). The optimal treatment strategy for such patients is not established.

“Many multidisciplinary groups currently use the 2-mm margin as an absolute indication for repeat surgery,” Dr. Kuerer said.

Drs. Tadros and Kuerer and their colleagues looked at the records of nearly 1,500 DCIS patients who underwent breast-conserving surgery at MD Anderson between 1996 and 2010. Some patients had undergone postoperative radiation therapy, and some had not; none had undergone repeat surgery. The researchers compared the locoregional recurrence rates of patients with negative surgical margins greater than or equal to 2 mm and patients with negative margins less than 2 mm in the radiation and no-radiation groups.

Among patients who had undergone radiation therapy, the locoregional recurrence rates of those with negative surgical margins greater than or equal to 2 mm and those with margins less than 2 mm did not differ significantly. But among patients who had not undergone radiation therapy, the locoregional recurrence rate of those with surgical margins greater than or equal to 2 mm (5.4%) was significantly lower than that of patients with margins less than 2 mm (30.9%; \( P = .003 \)).

“Patients with DCIS and margins less than 2 mm may not need repeat surgery if they receive radiation,” Dr. Kuerer said. “Each case needs to be evaluated by a multidisciplinary team, taking into account the patient’s age, the extent of margin involvement, and the patient’s preferences.”

The study’s report was recently published online in the *Annals of Surgery*. 

“Patients with DCIS and margins less than 2 mm may not need repeat surgery if they receive radiation.”

– Dr. Henry Kuerer