Radiation Therapy for Liver Cancer

Clinical trials expand treatment options for patients with primary liver cancer

By Sarah Bronson

Many patients with primary liver cancer could benefit from combination therapies that include radiation, but the central location of the liver requires exceptionally precise delivery of that radiation to avoid damaging healthy liver tissue or the adjacent organs. Innovative techniques enable the safe delivery of high doses of radiation to liver tumors, and clinical trials of these techniques are now enrolling patients with primary liver cancer.

The most common primary liver cancers are hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC), or cancer of the bile ducts. These diseases often develop in patients with inflammation or cirrhosis resulting from viral hepatitis, autoimmune disorders, or metabolic syndrome.

“Patients with primary liver cancer often have other comorbidities while they’re getting their radiation, and that often adds another layer of complexity to the management of these cases,” said Eugene Koay, M.D., Ph.D., an assistant professor in the Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center.

Dr. Koay is leading several clinical trials for patients with unresectable HCC or ICC. These trials aim to open up the option of radiation to new subpopulations of patients with liver cancer.

More precise radiation techniques

Modern conformal radiation modalities such as proton therapy or photon-based intensity-modulated radiation therapy (IMRT) help ensure the precise delivery of radiation to liver tumors. At MD Anderson, Dr. Koay and the gastrointestinal radiation oncology team are investigating the survival benefits and adverse effects of these treatments. IMRT is more commonly used but can cause collateral damage to healthy liver tissue and other organs. In contrast, proton therapy may deliver less radiation to healthy tissue surrounding the tumor, resulting in reduced liver toxicity and possibly better outcomes.

In a recent multi-institutional phase II trial, Dr. Koay and colleagues found that high-dose proton therapy can achieve high levels of tumor control and promising overall survival rates for both HCC and ICC patients. These doses were delivered safely thanks to a combination of technologies and techniques that were developed or refined in recent years and can be used with proton- or photon-based therapy.

One of these techniques is hypofractionated dosing, in which a high total radiation dose is delivered in a small to moderate number of high-dose fractions. Patients in the phase II trial received a median dose of 58 Gy in 15 fractions. This moderate number of...
fractions reduces the chance of dosimetric variation between fractions due to position changes or motion.

Another refinement, and one used in the phase II proton therapy trial, is motion management. Since the liver moves whenever a patient breathes, breath hold is used to keep the liver motionless while the patient receives radiation. However, Dr. Koay said, “The breath hold can vary from day to day, so we need some verification of where the tumor is in space.” With the use of three-dimensional image guidance, in which a computed tomography scan is taken while the patient is holding his or her breath in the treatment position, the tumor’s location can be confirmed so that adjustments can be made on a day-to-day basis.

The results of the phase II trial indicate that hypofractionated proton therapy and motion management can reduce the toxic effects of radiation therapy. Patients in the trial had a lower rate (3.6%) of worsening cirrhosis after radiation therapy compared with historical rates (23%) in trials that used photon-based stereotactic body radiation therapy.

Other innovations in radiation therapy used for primary liver cancer include simultaneous integrated boost with simultaneous integrated protection. This technique delivers an extremely high radiation dose to the tumor’s center, which often is more hypoxic than the peripheral tumor tissue and therefore more resistant to lower doses of radiation.

Also used at MD Anderson is a method called functional imaging, which allows radiation oncologists to pinpoint healthy liver cells. Healthy hepatocytes are accompanied by macrophages called Kupffer cells, which take up technetium-99m sulfur colloid. This agent can be used with single-photon emission computed tomography to localize those healthy cells in three dimensions, and radiation treatment plans can then be designed to avoid regions with high proportions of healthy hepatocytes to better preserve liver function.

**Phase III trial for HCC**

Patients with HCC are more likely to have cirrhosis than are patients with ICC; therefore, proton therapy may be a better option to treat patients with HCC without compromising their critical remnant of healthy liver. However, it has yet to be proven that HCC patients treated with proton therapy survive longer than those treated with IMRT. To compare overall survival between HCC patients given proton therapy and those given IMRT, Dr. Koay and colleagues designed a randomized phase III trial (No. NRG-GI003).

The multi-institutional phase III trial is now enrolling patients with unresectable or locally recurrent HCC. Dr. Koay said, “Our hypothesis is that the lower dose to the healthy liver in patients treated with proton therapy rather than photon therapy will translate to a survival advantage for the patients treated with protons.” Finding a substantial survival benefit would help justify the use of proton therapy, which can cost more than IMRT.

**Phase III trial for ICC**

The standard of care for unresectable ICC is chemotherapy alone; however, such treatment yields very low survival rates, and many patients receiving this care die within 18 months. To address these dismal outcomes, researchers at MD Anderson examined the mechanisms within the liver that led to the deaths of ICC patients and found that ICC tumors caused complications in the liver by closing off bile ducts or “squeezing” blood vessels and depriving the liver of nutrients.

Moreover, patients with ICC who received high-dose proton therapy in the recent phase II trial showed high 2-year overall survival rates compared with historical rates. “This is why giving higher doses of radiation would be thought to improve survival rates of these patients,” Dr. Koay said. “If you can control the growth of the liver tumor and prevent it from causing biliary obstruction or blood vessel disruption, then you might allow the patient to live longer.”

To test the hypothesis that radiation therapy can prolong survival for patients with unresectable ICC, Dr. Koay and colleagues are conducting a phase III trial (No. NRG-GI001). Patients in this trial first receive chemotherapy and then are randomly assigned to undergo either observation, chemotherapy and then are randomly assigned to undergo either observation, as is standard, or photon- or proton-based radiation therapy as determined by the treating physician. Demonstrating the efficacy of radiation in this trial would provide a new option to this patient group.

**Phase I trial for liver cancer with impaired liver function**

MD Anderson researchers also are exploring the potential use of radiation therapy in patients with liver cancer and compromised liver function due to advanced cirrhosis or previous treatment. Patients who undergo radiation therapy and have grade B or C cirrhosis (on the Child-Turcotte-Pugh scale) are at risk of developing radiation-induced liver disease, which can cause death within 6 months after irradiation.

To safely deliver radiation under these conditions, Dr. Koay and colleagues are using functional imaging to create radiation treatment plans that avoid healthy liver cells in a phase I trial (No. 2015-0052) for...
Proton Therapy for Breast Cancer May Avoid Heart Damage

Trial compares cardiotoxicity of proton- and photon-based radiation therapy to the breast/chest wall and lymph nodes

By Bryan Tutt

Radiation therapy to the whole breast or chest wall and the internal mammary lymph nodes can deliver a radiation dose to the heart that increases the risk of cardiovascular events. To see whether proton therapy can reduce this risk, a multi-institutional clinical trial is comparing proton therapy to standard photon-based radiation therapy for patients with locally advanced breast cancer.

“Breast cancer patients tend to be long-term survivors,” said Karen Hoffman, M.D., an associate professor in the Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center. “They have multiple decades ahead of them in which to face the consequences of treatment.” When a patient’s heart is irradiated, these consequences may include major cardiovascular events such as heart failure, coronary heart disease, myocardial infarction, valvular disease, arrhythmia, and unstable angina.

Despite efforts to reduce the radiation dose to the heart, the risk of cardiotoxicity from standard photon-based radiation therapy for breast cancer remains. “With the techniques we use at MD Anderson, our dose to the heart with photons is lower than published data nationally,” Dr. Hoffman said. “But protons have the potential to get that dose even lower.”

Head-to-head trial

Dr. Hoffman is MD Anderson’s principal investigator of the phase III RAD-COMP trial (No. 2016-0085), which is enrolling patients with node-positive breast cancer who have undergone mastectomy or lumpectomy and require radiation therapy to the whole breast or chest wall and the internal mammary lymph nodes. “Radiation therapy to the internal mammary node chain carries a high risk of cardiotoxicity because the chain runs right along the sternum,” Dr. Hoffman said.

Patients in the trial are stratified by age, baseline cardiovascular risk, type of surgery, and affected breast before randomization to ensure that equal numbers of patients in each subgroup receive proton- or photon-based treatment. Patients in both the proton and photon therapy groups receive a radiation dose of 45.0–50.4 Gy delivered in 1.8–2.0-Gy fractions.

The trial’s primary endpoint is major cardiac events, for which patients will be followed up for 10 years. “We can look at treatment plans and agree that proton therapy delivers a lower cardiac dose than standard therapy does,” said Elizabeth Bloom, M.D., a professor in the Department of Radiation Oncology and a co-investigator of the trial. “But we need to know if what we see on paper will translate into reduced long-term cardiac harm.”

The trial’s secondary endpoints include patient-reported fatigue, body image, and other quality-of-life measures. The researchers will also compare rates of locoregional control and overall survival, neither of which is expected to differ significantly between the patients treated with protons and those treated with photons.

Overcoming barriers

Drs. Bloom and Hoffman said that the chief barrier to recruiting patients for the trial is convincing insurance companies to cover the more expensive proton therapy. In theory, Dr. Bloom said, insurance companies might save money in the long run if their customers could avoid long-term health problems resulting from incidental radiation to the heart, lung, contralateral breast, and shoulder girdle muscles.

“Protons can help keep the radiation where it needs to be and minimize the doses to the heart and other structures,” Dr. Bloom said. “We think that this will have long-term health benefits, but we have to prove it. That’s the point of this trial.”

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For more information about the RAD-COMP trial, visit www.clinicaltrials.org and search for study No. 2016-0085.
New Targeted Therapies for Leukemia

New treatments target CD123, BCL2 proteins in acute myelogenous leukemia, blastic plasmacytoid dendritic cell neoplasm

By Bryan Tutt

Acute myelogenous leukemia (AML) and blastic plasmacytoid dendritic cell neoplasm (BPDCN) are aggressive and often fatal hematological malignancies. The cure rate for AML is around 50%, and patients who do not respond to first-line treatment or experience relapse have poor survival outcomes. Outcomes are even worse for patients with BPDCN, a rare malignancy with few approved treatments. But recently discovered molecular targets have led to new treatment options for AML, BPDCN, and other leukemias; and clinical trials of these treatments are under way.

“There have been several key, exciting developments in the past couple of years,” said Naveen Pemmaraju, M.D., an associate professor in the Department of Leukemia at The University of Texas MD Anderson Cancer Center. “A couple of novel therapeutic targets now enable us to offer targeted therapy for BPDCN patients, who have few treatment options, and for some AML patients.”

The therapeutic targets CD123 and BCL2 are proteins expressed at much higher levels on some leukemic cells than on healthy cells. Treatments that target CD123 are the subject of ongoing clinical trials for AML, BPDCN patients, and an agent that targets BCL2 is being used in clinical trials for AML patients and is being explored as a therapeutic option for BPDCN by Dr. Pemmaraju and colleagues.

**CD123**

CD123, a receptor for the immune cytokine interleukin-3, is overexpressed on the surface of some malignant cells, including the majority of AML and BPDCN cells. Clinical trials at MD Anderson are exploring the recombinant fusion protein SL-401, chimeric antigen receptor (CAR) T cells, and the drug-antibody conjugate IMGN632 as targeted therapies against CD123 for patients with AML and BPDCN.

**SL-401**

Current trials at MD Anderson are exploring SL-401 as a first-line therapy for BPDCN patients, as salvage therapy for BPDCN patients whose disease has persisted or recurred after standard chemotherapy, and as consolidation therapy for AML patients whose disease responded to standard chemotherapy.

SL-401 was the first anti-CD123 agent to be used in a clinical trial for patients with BPDCN (see “Blastic Plasmacytoid Dendritic Cell Neoplasm,” OncoLog, October 2015). In a pilot trial of SL-401, more than half the patients with BPDCN experienced a complete response.

These promising results led to a phase I/II trial of SL-401 (No. 2013-0979), which is currently enrolling patients with previously untreated or relapsed or refractory BPDCN at MD Anderson and other institutions.

In the current trial, patients receive an intravenous infusion of SL-401 on days 1–5 of each 21-day cycle. Patients continue treatment until disease progression or intolerable adverse effects occur.

The trial’s preliminary findings were presented at the American Society of Hematology’s annual meeting in December 2017 by Dr. Pemmaraju and colleagues, including Marina Konopleva, M.D., Ph.D., a professor in the Department of Leukemia and MD Anderson’s principal investigator of the trial. Of 32 evaluable patients with BPDCN, responses were seen in 27 (84%): 19 patients experienced a complete response, and eight experienced a partial response.

“SL-401 is a particularly active drug that has given us some hope and direction in this rare disease because almost all patients with BPDCN have leukemic cells that express CD123,” Dr. Pemmaraju said.

Dr. Konopleva is also leading a clinical trial (No. 2014-0860) of SL-401 as consolidation therapy for patients with AML who experienced a complete response (defined as less than 5% blast cells in the bone marrow) but have minimal residual disease or other risk factors for relapse and are not candidates for stem cell transplant. The goals of this phase I/II trial are to determine the maximum tolerated dose of SL-401, evaluate changes in minimal residual disease status, and assess relapse-free and overall survival. Dr. Konopleva and colleagues will also look for changes in the expres-

A skin lesion caused by blastic plasmacytoid dendritic cell neoplasm is shown before (left) and after (right) 4 weeks of treatment with the BCL2 inhibitor venetoclax. Images used with permission from Cancer Discov. 2017;7:156–164.
sion of CD123 and other stem cell and disease markers in bone marrow samples taken before and after treatment with SL-401.

**CAR T cells**

Another investigational treatment for patients with AML or BPDCN is UCART123, an off-the-shelf allogeneic CAR T cell product that is genetically engineered to target CD123. A multi-institutional phase I trial (No. 2016-0840) of UCART123 is now enrolling patients with newly diagnosed or relapsed or refractory BPDCN, and an additional treatment arm will soon begin enrolling patients with relapsed or refractory AML.

In the phase I trial, patients receive a cytotoxic lymphodepleting regimen, which destroys existing T cells and other lymphocytes that might interfere with the CAR T cells, followed by a single infusion of UCART123. The trial’s primary outcome measure is the safety of the novel treatment approach, with special emphasis on adverse events such as cytokine release syndrome, tumor lysis syndrome, and graft-versus-host disease, which are known to be associated with CAR T cell therapy for hematological malignancies.

“This is the first trial of CAR T cell therapy that was specifically initiated for patients with BPDCN,” Dr. Pemmaraju said.

**IMGN632**

IMGN632 combines an anti-CD123 antibody with a DNA alkylating agent. A first-in-human trial (No. 2017-0855) of this drug-antibody conjugate recently began enrolling patients with relapsed or refractory AML, BPDCN, and other CD123-positive hematological malignancies at MD Anderson. In the trial, researchers led by Hagop Kantarjian, M.D., a professor in and chair of the Department of Leukemia, seek to find the maximum tolerated dose of IMGN632 and the recommended dose for future trials. The researchers will also observe IMGN632’s ability to provoke an immune response.

**BCL2**

As is the case with CD123, the anti-apoptotic protein BCL2 is expressed at higher levels by AML, BPDCN, and other leukemia cells than by normal cells. The BCL2 inhibitor venetoclax is approved by the U.S. Food and Drug Administration to treat relapsed chronic lymphocytic leukemia and has shown activity against AML in clinical trials at MD Anderson and elsewhere.

Current trials are exploring combinations of venetoclax with other treatments for AML in various subsets of patients. “We feel that venetoclax is a general sensitizer to many types of therapies, and its favorable safety profile makes it easy to combine with many types of treatments,” Dr. Konopleva said.

In one trial (No. 2016-0979), patients 18–65 years old with newly diagnosed or relapsed or refractory AML receive venetoclax with the standard intensive chemotherapy regimen fludarabine, cytarabine, filgrastim, and idarubicin (FLAG-IDA). This phase I trial, led by Courtney DInardo, M.D., an assistant professor in the Department of Leukemia, will evaluate the safety and tolerability of the drug combination and make a preliminary assessment of the regimen’s efficacy.

Other trials are evaluating venetoclax combinations in patients 60 years or older with AML who cannot tolerate standard intensive chemotherapy regimens. One of these trials (No. 2015-0898) is evaluating the safety and efficacy of venetoclax in combination with either cobimetinib, which inhibits the MEK kinase pathway, or idasanutlin, a small-molecule inhibitor of the oncoprotein MDM2. Dr. Konopleva and colleagues, including Naval Daver, M.D., an associate professor in the Department of Leukemia, presented the preliminary results of the nonrandomized trial’s dose-escalation phase at the American Society of Hematology’s annual meeting in December 2017. The overall response rates (complete responses plus complete responses with incomplete platelet recovery or incomplete hematological recovery) were 20% and 33% for the cobimetinib and idasanutlin arms, respectively. For both treatment arms, however, the response rates were higher for patients treated with the doses that will be used in the trial’s expansion phase than for patients treated with lower doses.

Two phase III trials of venetoclax focus on treatment-naïve AML patients 60 years or older who are ineligible for standard chemotherapy because of age (75 years or older) or comorbidities. In one trial (No. 2016-0985), patients are randomly assigned to receive the hypomethylating agent azacitidine plus venetoclax or placebo. In the other trial (No. 2017-0398), patients are randomly assigned to receive low-dose chemotherapy with cytarabine plus venetoclax or placebo.

“Combinations of venetoclax with low-dose cytarabine or a hypomethylating agent show tolerable safety profiles and very exciting activity for elderly AML patients who are unable to undergo intensive chemotherapy,” Dr. Konopleva said.

To assess whether venetoclax might also be effective against BPDCN, a multi-institutional group of researchers including Drs. Pemmaraju and Konopleva tested venetoclax in BPDCN cell lines and mouse models. After these preclinical studies confirmed the drug’s activity, Dr. Pemmaraju and his colleagues offered venetoclax as an off-

**“The combination of CD123 or BCL2 inhibition with various other treatment strategies will likely play an important role in the treatment of AML and BPDCN.”**

– Dr. Marina Konopleva
Two patients treated with venetoclax were pursuing a clinical trial of the drug for patients with BPDCN,” Dr. Pemmaraju said. He said the trial may begin enrolling patients this spring.

Moving forward
More clinical trials of treatment combinations that target CD123 or BCL2 are on the horizon for patients with AML or BPDCN. For example, SL-401 combined with the hypomethylating agent azacitidine showed synergy against AML in preclinical studies, and a clinical trial of this combination for patients with relapsed AML is expected to open soon.

In addition, the outcomes of current trials of venetoclax with various treatments in other hematological malignancies might eventually lead to trials of similar combinations in patients with AML or BPDCN. One ongoing trial (No. 2017-0025) for patients with B cell lymphomas combines venetoclax with etoposide, cyclophosphamide, and doxorubicin at doses that are adjusted for each cycle plus prednisone, vincristine, and rituximab. Another trial (No. 2015-0860) combines venetoclax with the BTK inhibitor ibrutinib for patients with chronic lymphocytic leukemia.

“The combination of CD123 or BCL2 inhibition with various other treatment strategies will likely play an important role in the treatment of AML and BPDCN,” Dr. Konopleva said. “Our task will be to determine which subpopulations of patients are most likely to benefit from which treatment combinations.”

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FURTHER READING

Supportive Care for Cancer Patients

Supportive care is a relatively new but very important part of cancer treatment. Supportive care services address physical, emotional, and spiritual problems that may affect patients’ quality of life or ability to function. These services are provided before and during cancer treatment and are tailored to meet the needs of individual patients.

“Supportive care covers all aspects of physical and emotional suffering that occur during cancer treatment,” said Eduardo Bruera, M.D., a professor in and chair of the Department of Palliative, Rehabilitation, and Integrative Medicine and medical director of the Supportive Care Center at The University of Texas MD Anderson Cancer Center. “In supportive care, we treat the whole person.”

What is supportive care?

Supportive care helps patients deal with a variety of physical and emotional challenges. These challenges are different for each patient. “Some patients have pain and fatigue as the main problems,” Dr. Bruera said. “Others have emotional or spiritual distress or communication issues with parents or young children.”

Supportive care is similar to palliative care, which is often given to ease the suffering of patients with advanced cancer. The difference between the two, according to Dr. Bruera, is that supportive care can begin as soon as a patient is diagnosed with cancer. “We look at such care in three stages,” Dr. Bruera said. “The early stage is supportive care. For patients whose cancer does not respond to treatment or returns, the later stage is palliative care. And for patients near the end of life, the last stage is hospice care.”

The use of supportive care has grown steadily as doctors increasingly realize how disruptive cancer and its treatment can be for patients. While the goal of cancer treatment is to get rid of the patient’s cancer, the main goal of supportive care is to improve the patient’s quality of life.

Supportive care services

Dr. Bruera said that MD Anderson was the first cancer hospital in the United States to establish a supportive care center. Since then, many major cancer hospitals have established supportive care centers modeled after MD Anderson’s. And even hospitals without designated supportive care centers may provide some supportive care services. Cancer patients at such hospitals can ask their treatment team or hospital patient advocate which services are available and how to access them.

At MD Anderson, both inpatients and outpatients can be referred to the Supportive Care Center by their cancer treatment team at any time during cancer treatment or even before treatment begins. Patients in the Supportive Care Center receive treatment from a team that may include doctors and nurses who specialize in supportive and palliative care; pharmacists; counselors such as psychologists and social workers; and chaplains.

The supportive care team can also refer patients to other specialists, such as pain management specialists or physical rehabilitation experts. Close collaboration between the supportive care team, the cancer treatment team, and other specialists helps ease patients’ suffering while patients receive the best possible treatment for their cancer.

Another important aspect of supportive care is meeting the needs of patients’ family members, especially those who act as caregivers. Cancer and its treatment can be as stressful for caregivers as for patients, and the supportive care team’s social workers and chaplains give these caregivers the support and resources they need to manage that stress.

“It’s very important for patients and their families to know that we understand that there are issues of physical, emotional, family, and spiritual distress in addition to the cancer itself. It’s normal to have those problems when one is diagnosed with cancer,” Dr. Bruera said. “The beauty is that this care is accessible at any moment after the diagnosis of cancer.”

For more information

• Ask your physician
• Call askMDAnderson at 877-632-6789
• Visit MD Anderson’s Supportive Care Center at http://bit.ly/2fv5l3G

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Radiation Therapy for Liver Cancer
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patients with primary or metastatic liver tumors.

“Historically, patients with impaired liver function would not come to our department because of the risk of radiation toxicity,” Dr. Koay said. “But by doing this trial, we’re hoping to open up another treatment option for these patients who otherwise don’t have any good options left.”

Hoped-for changes in standard care

Although radiation therapy to the liver carries risks, more and more indications for radiation to treat various liver cancers have been identified over time, and researchers at MD Anderson hope to continue developing strategies to safely administer powerful radiation treatments to patients with liver cancer who lacked that option in the past. For patients who cannot undergo surgery, radiation therapy could provide comparable relief, especially when precise delivery techniques are used.

Dr. Koay said, “We’re hoping to establish radiation as part of the standard of care for both ICC and HCC and to substantially prolong the survival of these patients.”

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FURTHER READING


“Our hypothesis is that the lower dose to the healthy liver in patients treated with proton therapy rather than photon therapy will translate to a survival advantage.”

– Dr. Eugene Koay

For more information about clinical trials for patients with liver cancer, visit www.clinicaltrials.org.