WINTER 2015, VOL. 4, NO. 1

Pathways in Cancer

Clinical insight and analysis in advanced cancer care

Transarterial Radioembolization: Image-Guided Yttrium-90 Microsphere Therapy for Unresectable Hepatic Tumors

Mazyar Ahmadi, MD

Colorectal cancer is the fourth most commonly diagnosed malignancy in the industrialized nations and at least 60 percent of the nearly 150,000 Americans diagnosed each year will see their cancer spread to the liver. Studies have shown that two out of three patients with liver metastatic disease die of liver failure, and most liver tumors cannot be surgically resected. This leaves a delicate situation for physicians as they consider treatment options. The key is to fully understand the multidisciplinary tools at our disposal to make an impact on the lives of these patients.

Transarterial Radioembolization (TARE) has recently emerged as a fully FDA-approved treatment option for patients with colorectal cancer that has spread to the liver, and has also been approved to be used under a humanitarian device exemption for treatment of patients with hepatocellular carcinoma (HCC). Mercy Radiology Group, as part of Dignity Health Medical Foundation, now offers liver directed radioembolization for patients with primary and metastatic cancer to the liver.

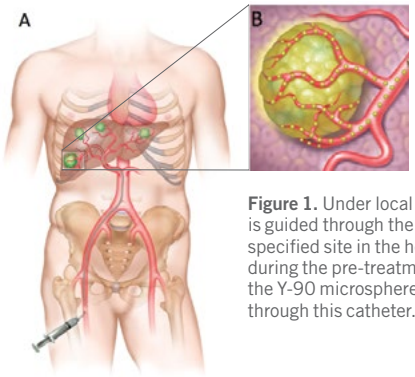

Figure 1. Under local anesthetic, a microcatheter is guided through the arterial system (A) to pre-specified site in the hepatic artery as identified during the pre-treatment planning session, where the Y-90 microspheres (B) are then administered through this catheter.

Typical TARE treatment involves delivering millions of microscopic radioactive spheres directly to the tumor site via a catheter inserted in the common femoral artery and advanced to the branches of the hepatic artery supplying the neoplasm (Fig 1). These microspheres contain the radioactive isotope Yttrium-90 (Y-90), thereby selectively targeting liver tumors with a dose of internal radiation up to 40 times higher than conventional radiotherapy while sparing healthy tissue. This is due to short distance of action of this particular type of radiation; high-energy beta particles that travel about 3 mm on the average in the soft-tissue. Given the short Y-90 half-life of 2.67 days, approximately 95% of the radiation dose is delivered within 11 days from treatment administration. Patients are usually able to go home three to six hours after the procedure, and the reported side effects are few. Patients may experience flu-like symptoms for a period of one to two weeks after the procedure.

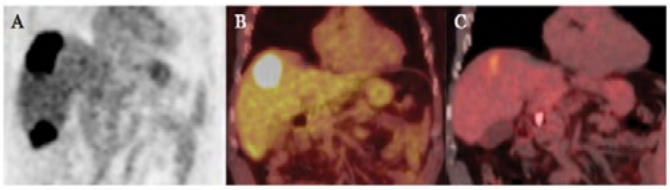

Figure 2. 64-year-old male with metastatic colon cancer status-post systemic chemotherapy with great initial response presented with progression of disease on surveillance imaging. Coronal PET image (A) shows two FDG avid metastatic lesions in the right lobe of liver at baseline, with partial response of superior and near complete response of inferior lesion two-months post initial TARE treatment (B), and near complete resolution of superior and complete response of inferior lesion five-months post second TARE treatment (C).

TARE has been shown to be an effective modality for metastatic liver cancer patients who are (heavily) pre-treated or are not candidates for surgical resection due to the size, distribution or accessibility of the tumors (Fig 2). Furthermore, literature suggests radioembolization to be effective in treating other forms of liver cancer such as HCC, as well as liver metastases from other primary sources. In case of HCC, TARE has been used as neoadjuvent therapy prior to resection or transplantation, or in conjunction with intravenous chemotherapy in non-surgical patients. In fact, since 2004, the National [US] Comprehensive Cancer Network (NCCN)

continued on page 2

Treating Hepatocellular Carcinoma with Stereotactic Body Radiation Therapy

Ellen Wiegner, MD

Hepatocellular carcinoma is a highly aggressive malignancy with approximately 30,000 cases diagnosed and 22,000 deaths in the United States annually. Surgery is the primary curative therapy. For patients with adequate liver function and a solitary liver tumor, partial hepatectomy results in a 5-year overall survival of 50-70%. For highly selected patients who are not candidates for partial hepatectomy, orthotopic liver transplantation is an alternative curative option, though many patients progress while awaiting a donor organ. The majority of patients are not eligible for surgery due to disease stage or underlying liver dysfunction. Therefore, several non-surgical local therapies have been developed including radiofrequency ablation, transarterial chemo-embolization (TACE), transarterial radioembolization (TARE), percutaneous ethanol injection, and more recently stereotactic body radiation therapy (SBRT).

Historically, radiation therapy has not been utilized as a primary treatment for HCC due to the risk of developing radiation induced liver disease with relatively low dose radiation. SBRT is a recent advancement in radiation treatment which delivers highly conformal radiation therapy to a tumor target while limiting radiation exposure to normal adjacent tissues. Using SBRT, we are now able to deliver ablative doses of radiation to liver tumors while sparing the adjacent normal liver tissue resulting in acceptable rates of hepatotoxicity in patients with adequate liver function (Childs Pugh Class A). For patients who are not candidates for other local ablative procedures due to size or location of tumor(s), SBRT is a viable alternative treatment.

Several retrospective studies evaluating SBRT for HCC have demonstrated promising results with 2-year local control rates ranging from 55-75% and 2-year overall survival of 61-67%. The largest phase I/II prospective study to date was conducted at The Princess Margaret Hospital in Toronto. This study enrolled 102 patients with relatively advanced disease, including 56 patients who had failed after prior local therapy, 62 patients with multiple liver tumors, and 56 with tumor vascular thrombosis. Despite this unfavorable patient population, the 1-year local control rate was 87% and median survival was 17 months. Although SBRT can achieve high local control rates, disease progression outside of the targeted area remains a significant issue highlighting the importance of effective systemic therapy.

The NRG oncology group is conducting a phase III clinical trial comparing SBRT and sorafenib to sorafenib alone in patients with HCC not suitable for or refractory to other local therapies (RTOG 1112). The available data suggest that SBRT is a very effective local ablative procedure with favorable toxicity profile. Based on these data, the National Comprehensive Cancer Network (NCCN) guidelines currently recommend SBRT be considered as local ablative treatment for patients who are not surgical candidates. Ongoing clinical trials will further define the role of SBRT in treating HCC in the future.

Transarterial Radioembolization: Continued from page 1

has included Y-90 microspheres treatment in its clinical guidelines for unresectable primary liver cancer.

Y-90 microspheres treatments have shown to extend patient survival with multiple studies independently reporting overall survival benefit of 8-29 months, depending on treatment strategies which range from first-line treatment to salvage therapy. Other studies concentrating on the safety and tolerability, tumor response, and survival of patients have shown strong response rates for heavily pretreated patients as well as improved quality of life. The incidence of post-embolization syndrome after radioembolization therapy is up to four times lower and less severe compared to traditional transarterial chemo-embolization, resulting in significantly greater quality of life observed for Y-90 treated patients at short-term follow-up.

We are excited to provide liver-directed Y-90 radioembolization as a new treatment option to be used in a multidisciplinary approach with the goal of extending survival time, improving quality of life, and providing new hope to our patients with primary and metastatic liver tumors.

The Changing Spectrum of Systemic Management for Hepatocellular Cancer

Robert Quadro, MD

Chemotherapy has been the mainstay of therapy for cancers with widespread metastatic disease. The rationale, of course, is that giving a therapy which enters the bloodstream would penetrate everywhere the cancer cells happen to be. The disadvantage, however, is that almost all chemotherapeutic agents work by compromising the DNA replication mechanisms and therefore require cell division to kill the cancer cells. This has proven to be a somewhat effective strategy for rapidly growing cancers in which, at any one given time, a significant percentage of cells are undergoing mitosis and are therefore affected by the treatment regimen. For other cancers characterized by slower growth patterns, chemotherapy has proven to be much less effective. Such was the case for hepatocellular cancers in which chemotherapy has proven to be very disappointing, having response rates in the 15-20% range and providing an overall survival benefit measured in weeks rather than months.

The advent of targeted therapies has changed the paradigm for the management of many cancers. Unlike chemotherapy, these agents target enzymes in metabolic pathways which cancers need to grow. Because all of the cells in a particular tumor require these pathways, targeted therapies are effective whether or not the cells happen to be undergoing cell division at the time of exposure to these agents. Targeted therapies include small molecule enzyme inhibitors (usually tyrosine kinase inhibitors) and large molecule monoclonal antibodies which attack tumors at specific targets. Some targeted treatments (like imatinib in CML) target a very specific target, while others block multiple pathways.

The results for chemotherapy in hepatocellular cancer have been disappointing for several reasons. Hepatocellular cancers often express genes which code for resistance to chemotherapy (including p-glycoprotein and mutations in p53.) Many patients with advanced hepatoma have a compromised ability to tolerate chemotherapy because of underlying liver disease making chemotherapy very challenging. For this reason the mainstay of therapy for hepatocellular cancer has been surgical management or local therapies such as chemoembolization which are really most suitable for patients with early disease but not for patients with more widespread metastasis.

The introduction of the targeted therapy for hepatocellular cancer was a major step forward in the therapy for these patients. Several factors about this cancer suggested that it might be an ideal candidate for this type of treatment. Preclinical work suggested that epithelial growth factor pathway (a common pathway for carcinogenesis and cell proliferation) played a role in the genesis of HCC. Hepatomas are highly vascular tumors with high levels of expression of vascular endothelial growth factor (VEGF), suggesting that VEGF inhibitors would be an effective therapy. Finally a third pathway, the Raf/MAP kinase (MEK/ERK) pathway has also been implicated in the genesis of HCC. There are targeted strategies to inhibit each of these pathways.

The first targeted therapy to be introduced for HCC is the drug sorafenib. This is a small molecular weight tyrosine kinase inhibitor which inhibits Raf kinase and the VEGF intracellular pathway. The SHARP trial, conducted in Europe, evaluated patients with good performance status (Child-Pugh A or B) who had inoperable hepatocellular cancer. Overall survival was significantly improved as compared to best supportive care (10.7 months vs 7.9 months.) The drug was relatively well tolerated with a side effective profile which is different from common chemotherapy side effects (the most common effects seen were "hand/foot syndrome" and diarrhea—both of which were readily manageable.) Interestingly, in this study, objective tumor responses were very low, underscoring an important point about targeted therapy. Because the mechanism of action is metabolic pathway inhibition rather than the killing of rapidly dividing cells, tumors tend not to shrink, and can even increase slightly in size. Yet despite this, the quality of life and overall survival of the patient can be markedly improved. Clearly we need new ways of thinking about what constitutes a response when using these agents.

Obviously, despite this breakthrough, the life expectancy of patients with advanced HCC is still measured in months. New directions include newer targeted therapies trying to inhibit as many metabolic pathways as possible. We also need to be able to better evaluate which of those metabolic pathways are crucial to a particular cancer's survival.) Because the side effect profile of targeted therapies is different than conventional chemotherapies, the idea of combining the two modalities is being explored.

A final use of targeted therapies is in patients who have earlier stage disease but in whom definitive therapy (such as liver transplantation) cannot occur right away (such as patients who are on a waiting list for a donor liver). Targeted therapies can provide a way of "bridging" the patient, essentially buying time, halting tumor progression, until such time as a more definitive therapy can be administered.

Dignity Health
Cancer Institute of Greater Sacramento

6501 Coyle Avenue
Carmichael, CA 95608

TUMOR BOARDS

Dignity Health Cancer Institute of Greater Sacramento's multidisciplinary approach to cancer care includes regularly scheduled Tumor Boards held throughout Greater Sacramento, offering clinical review of patient cases for optimal treatment results. For each of our Tumor Boards, physicians are eligible for 1 CME credit.

To present a case at an upcoming Tumor Board, please email, fax, or call contacts noted below. To present a case, please provide:

- **Patient's name**
- **Date of birth and/or medical record number**
- **Disease site**
- **Diagnosis**
- **Where path and imaging can be found**

Hospital Cancer Conferences

Mercy General Hospital
Wednesdays at 12:15 p.m.
Location: Greenhouse Conference Room

Contact: Renae Huwes
renae.huwes@dignityhealth.org
916.536.3157 (phone)
916.536.3044 (fax)

Mercy Hospital of Folsom
4th Wednesday of every other month at Noon
(January, March, May, July, September, November)
Location: CC1 and 2 or PCU conference room

Contact: Mansoor Javeed, MD
mansoor.javeed@dignityhealth.org
916.984.6230 (phone)

Mercy San Juan Medical Center
Thursdays at 12:30 p.m.
Location: Conference Room 2

Contact: Renae Huwes
renae.huwes@dignityhealth.org
916.536.3157 (phone)
916.536.3044 (fax)

Methodist Hospital of Sacramento
3rd Friday of each month at Noon
Location: Bistro Conference Room

Contact: Starr Fesler
sfesler@uscmc.com
916.683.9616 (phone)

Sierra Nevada Memorial Hospital
Thursdays at 12:30 p.m.
Location: OPC 110-120

Contact: Debby Kirk
debby.kirk@dignityhealth.org
530.274.6872 (phone)

Woodland Healthcare
Tuesdays at 12:15 p.m.
Location: DCR 5

Contact: Michelle Ing, PA
michelle.ing@dignityhealth.org
530.662.3961 (phone)

Tumor-specific Cancer Conferences

Breast Cancer Conference
3rd Friday of each month at 12:30 p.m.
Location: Mercy Cancer Center
3301 C Street, Suite 550
Large Conference Room

Contact: Renae Huwes
renae.huwes@dignityhealth.org
916.536.3157 (phone)
916.536.3044 (fax)

GU Cancer Conference
4th Tuesday of each month at 7:30 a.m.
Location: Mercy San Juan, CC3

Contact: Renae Huwes
renae.huwes@dignityhealth.org
916.536.3157 (phone)
916.536.3044 (fax)

Cases may be brought directly to the conference. Pathology and imaging will not be routinely ordered unless there is a question regarding the results.

Thoracic Cancer Conference
2nd Wednesday of each month at 4 p.m.
Location: Mercy San Juan, CC3

Contact: Renae Huwes
renae.huwes@dignityhealth.org
916.536.3157 (phone)
916.536.3044 (fax)

Cases may also be brought directly to this conference.