

Clinical Interventional Oncology Symposium And Integrative Healthcare Symposium

Walter Alexander

Clinical Interventional Oncology Symposium

This year's ninth annual Clinical Interventional Oncology gathering attracted 400 multidisciplinary specialists to Hollywood, Florida, on February 4 and 5 and featured a two-day program on the latest interventional treatments. The reports below focus on a session devoted to "Liver-Directed Therapy and the Role of Y-90 [Yttrium-90]."

The Role of Y-90 for Neuroendocrine Tumors

- Timothy Clark, MD, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Overall survival rates among patients with neuroendocrine tumors (NETs) treated with transarterial radioembolization with Y-90, a beta-emitting radionuclide, appear to be equal to rates for those treated via transarterial chemoembolization (TACE) or transarterial embolization (TAE). Toxicity is lower for Y-90, however, and unlike TACE and TAE, Y-90 radioembolization can be performed as an outpatient procedure.

Both TAE and TACE reduce blood flow to NETs, leading to tumor ischemia and necrosis. Delivery of Y-90–bonded resin or glass microspheres leads to both embolization of vasculature and exposure of tumor tissue to the beta-emitting radionuclide. Y-90 radioembolization (also known as selective internal radiation therapy) is performed via transfemoral or transradial catheterization of the hepatic artery to the tumor vasculature. Treatment with Y-90, Dr. Clark said, is indicated for progressive, large, or symptomatic NETs, tumors that are functioning (producing secretions that lead to clinical symptoms), and/or tumors with mass effect (compression of adjacent organs or tissues). "Embolization does quite well, particularly for early-stage, well-differentiated G1 [grade] tumors," he said.

Objective response rates with Y-90 embolization (55% to 60%) are as good as those reported for alternative chemotherapies, such as capecitabine/temozolomide (CapTem) (60%), and better than rates for everolimus (less than 5%) or peptide receptor radionuclide therapy (PRRT) (15% to 35%). Progression-free survival (PFS) for embolization in G1 tumors is 18 months compared with 11 months and 14 months for everolimus and CapTem, respectively. While PFS is longer with PRRT (30–40 months), toxicity in U.S. studies of late-stage disease in PRRT has been high (69% marrow, 25% renal, 31% hepatic). Toxicity for Y-90 embolization is in the 8% to 11% range, while everolimus is in the 5% to 9% range, and CapTem toxicity is approximately 11%.

"For disease control, Y-90 has had a pretty strong track record," Dr. Clark said, noting that rates with Y-90 over

12 studies for complete or partial responses are just over 50% (mostly partial responses), and stable disease or better is achieved in more than 80% of patients.¹

A 2012 systematic review of 12 studies comparing Y-90 with TACE found that Y-90 required fewer treatments (1.5 versus 2.2) and had a 63% response rate versus 58% for TACE, with lower disease progression (4% versus 9%). While biochemical responses were greater with Y-90 (86% versus 73%), median overall survival (OS) was longer with TACE (35 months versus 28 months).²

A recent analysis of predictors of Y-90 response by Fan and colleagues revealed that survival was shorter in patients who had received prior systemic therapy ($P = 0.015$) and multiple Y-90 treatments ($P = 0.046$) and that radiographic response was greater in those with a tumor burden greater than 33%. In addition, patients with islet cell tumors lived longer than those with carcinoid tumors. The review was based on eight-year experience in 38 NET patients with median follow-up of 17 months and median survival time of 29.2 months.³

In contrast to Fan et al., another recent retrospective review that included 155 NET patients treated over 11 years reported longer OS among patients with a tumor burden of less than 50%. OS was longer for TACE/TAE than Y-90 according to a Cox model (hazard ratio [HR], 2.1; $P = 0.02$) and equivalent according to a proportional hazards model (HR, 1.8; $P = 0.11$). Hepatic PFS was similar for all patients.⁴

Short-Form (36) Health Survey scores for mental and social domains in a quality-of-life analysis among 30 Y-90 patients by Cramer et al. were higher than typically found in the U.S. general population at six, 12, and 24 months.⁵

"While this therapy is equivalent to other NET transarterial therapies in overall survival, it does have significant benefits in being achievable in an outpatient setting with reductions in clinical toxicity and preserved quality of life out to two years in emerging studies," Dr. Clark concluded.

The Role of Y-90 for Metastatic Colorectal Cancer

- Daniel B. Brown, MD, Director of Interventional Oncology, Vanderbilt University School of Medicine, Nashville, Tennessee

Most of the recent and ongoing clinical research in Y-90 radioembolization of unresectable metastatic colorectal cancer (CRC) has been in patients with liver-only or liver-predominant disease receiving first- and second-line treatment in combination with the regimens of folinic acid/fluorouracil (5-FU)/oxaliplatin (FOLFOX), folinic acid/5-FU/irinotecan (FOLFIRI), or 5-FU/leucovorin. Y-90 therapies, however, are most commonly used as salvage therapy, according to Dr. Brown. "Y-90 use has increased year by year in part because it's less toxic than

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other interventional radiology treatments of liver cancer, such as chemoembolization, and can treat larger disease burdens than tumor ablation, with easier recovery,” he said in an interview.

In a review of clinical trial results for both glass and resin Y-90 microspheres, Dr. Brown cited a phase 2 trial in which first-line 5-FU/leucovorin therapy was compared with and without the addition of Y-90 resin microspheres (SIR-Spheres, Sirtex Medical) in 21 chemotherapy-naïve patients with advanced CRC. In that study, response, time to progression (TTP), and median survival favored the Y-90 treatment arm (response, 72.7% versus 0% [using RECIST criteria]; $P < 0.001$) (TTP, 18.6 months versus 3.6 months; $P < 0.0005$) (median survival, 29.4 months versus 12.8 months; $P = 0.02$).⁶

The SIRFLOX trial, which led to the U.S. approval for resin Y-90 microspheres, compared first-line modified FOLFOX with or without Y-90 and with or without bevacizumab (Avastin, Genentech) in 518 patients with unresectable liver-only or liver-predominant metastatic CRC. While progression-free survival (PFS) did not improve significantly with the addition of Y-90 (10.7 months versus 10.2 months; $P = 0.43$), median TTP in the liver was delayed significantly by 31% with the Y-90 combination (20.5 months versus 12.6 months; $P = 0.002$).⁷

PFS and overall survival rates for Y-90 in other combination trials have been superior to historical rates for their non-Y-90 components. (e.g., with irinotecan, 5-FU/leucovorin, or cetuximab [Erbix, Lilly]). In addition, in a 2012 retrospective comparison with best supportive care of salvage use of Y-90 among 339 patients (approximately two-thirds of whom had CRC), overall survival was significantly longer (11.9 months versus 6.6 months; $P = 0.001$). Mortality risk was much higher (hazard ratio, 1.8) in patients with greater than 25% liver replacement by tumor.

The phase 2, multicenter SITILO study reported 12.6-month median survival with Y-90 resin microspheres among 50 very heavily pretreated patients with unresectable chemorefractory CRC. The survival rate exceeded that of irinotecan either alone or in combinations in second-line therapy.⁸ “That is a very positive finding,” Dr. Brown said, noting that all patients had previously progressed on FOLFOX/FOLFIRI, 50% had received four prior regimens, 60% had 25% to 50% liver involvement, and 70% had bilobar disease. Citing a list of clinical trials with third-line or later treatments, all with shorter survival than with Y-90 in SITILO, Dr. Brown commented: “This, to me, argues that we should be pursuing trials looking at combining Y-90 and systemic therapy and biologic therapy. There’s potential to improve survival for all of the patients we see.”

The RESIN registry, Dr. Brown said, is now collecting data on a wide range of Y-90 treatment combinations (e.g., chemotherapy, systemic immunotherapies, biologics) and currently has 27 sites open to enrollment and 350 entered patients. RESIN will allow researchers to spot promising time-to-progression findings.⁹ “This will help shape strategies for future prospective randomized trials,” he said.

EPOCH, a phase 3 trial of glass Y-90 microspheres (TheraSphere, BTG International) in 360 CRC patients with liver metastases, is still enrolling,¹⁰ and data from FOXFIRE, a trial tracking survival outcomes of FOLFOX with or without a biologic agent and with or without Y-90 resin spheres, are due this spring.¹¹

Percutaneous Rose Bengal as an Oncolytic Immunotherapy for Hepatic Metastases

- Paul M. Goldfarb, MD, Oncology Associates of San Diego, San Diego, California

PV-10 (10% rose bengal disodium for injection), an intralesional chemoablative agent, may serve effectively as a therapeutic bridge to transplant for some hepatocellular carcinoma (HCC) patients, according to the results of a preliminary treatment series. The basket study of PV-10 oncolytic immunotherapy, which included patients with tumors originating in a variety of locations, also revealed that outcomes for gastrointestinal lesions were especially encouraging, with “intriguing” long-term survival among some patients with poor-prognosis metastatic colorectal cancer.

“PV-10 is minimally invasive, it doesn’t appear to injure surrounding liver tissues, and we haven’t observed significant scarring,” Dr. Goldfarb said. He also noted in an interview at his poster presentation that HCC treatment has changed in recent years, with transplantation becoming the primary mode of therapy, and therapies that serve as a bridge to transplant becoming of greater interest. He added, “Unlike radioembolization, which delivers yttrium-90 beads through the vasculature to an entire region of the liver, this strategy limits exposure to PV-10 to just the intended specific area of the tumor.”

Intralesional injections of PV-10, Dr. Goldfarb said, cause rapid disruption of tumor cells and immunogenic cell death, leading to T-cell priming and activation and evidence of eventual remote tumor regression. Most clinical testing of PV-10 has been in cutaneous melanoma, where it has demonstrated high rates of complete response and durable local control. A phase 3 trial in melanoma is in progress with PV-10 versus chemotherapy or oncolytic virus therapy.

The PV-10 series included 16 patients with hepatic lesions (five metastatic colorectal cancer patients with liver metastases and six HCC patients), two lung cancer patients, and one patient each with pancreatic cancer, ovarian cancer, and melanoma. Patients with at least one liver tumor 1 cm or greater in size received a single intralesional injection of PV-10 to a designated target lesion. After assessment at 28 days, patients could receive sequential injections to other tumors.

“The patients had smaller lesions, and we were able to treat them completely,” Dr. Goldfarb said. “We had multiyear good disease control at a rate certainly as good as surgical resection.” Four of the five metastatic colorectal cancer patients with hepatic tumors were alive nine to 73 months after treatment, including one with no evidence of disease at month 73. The fifth, with multifocal disease, died from disease progression at three months. Dr. Goldfarb commented, “It’s simpler than doing radiofrequency or microwave or external radiation, and because the needle is dramatically smaller, there appears to be less risk of seeding. Also, it doesn’t preclude your coming back later and doing a surgical resection or other procedure.”

Two HCC patients remain alive at 75 and 58 months (the former with no evidence of disease), and five have died (two to 48 months after PV-10 treatment). Two lung cancer patients with extensive multifocal disease died four and 12 months after PV-10 treatment.

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Dr. Goldfarb pointed out that while PV-10 will ablate HCC lesions, it does not necessarily address the underlying disease because potential immunogenic effects may not occur universally. In addition, PV-10's mechanism is appropriate for cancers that appear as isolated solid lesions as occurs in hepatic and renal cancers and melanoma. For these it may offer a good chance of long-term remission. "My impression is that this therapy is agnostic to histology and works regardless of the histology of the primary tumor. Its utility may be limited for breast cancer or other cancers, which tend to be multifocal."

Toxicity was generally transient (injection site reactions, one patient with photosensitivity, and one with lethargy). One elderly patient with an 8.9-cm HCC lesion died of an apparent thrombus not attributed to treatment. Expansion cohorts are assessing activity in multiple hepatic tumor types.

Future research, Dr. Goldfarb suggested, could have surgical resection or thermal ablation as comparators with non-inferiority as the primary outcome measure. The goal would be to demonstrate that PV-10 chemoablation offers a simpler, more straightforward approach.

"All of this needs to be corroborated. But as an initial study, I think this is quite encouraging," Dr. Goldfarb concluded.

Integrative Healthcare Symposium

The Integrative Healthcare Symposium, an annual meeting of multidisciplinary practitioners of functional and integrative medicine, was held February 23–25 in New York. Reviewed below is a presentation by an anesthesiologist who has staked out a controversial position against routine use of opioids for chronic pain.

Managing Chronic Pain: The Age Before and After Opioids

- Jane C. Ballantyne, Professor of Medicine, University of Washington, Seattle, Washington

Lessons drawn from the epidemic of opioid addiction include strong recommendations against opioid use for chronic pain, according to Dr. Ballantyne, who spoke during a panel discussion entitled "Pain, Prejudice, and Opioids: Emerging Policy and Integrative Practice."

"Use of opioids for chronic pain misunderstands chronic pain. If we can teach people to live well with chronic pain and provide them with the right tools, that is the best we can do," she said. "The overprescribing of opioids in the 1990s and 2000s produced the worst iatrogenic catastrophe ever ... Opioids have a very limited role in the treatment of chronic pain because they carry enormous risk and have not been shown to be beneficial if used continuously long term."

Dr. Ballantyne's opposition to the routine use of opioids in chronic pain, especially the use of pain intensity scales as absolute guides to opioid prescribing, has roots in the work of H. K. Beecher, who identified as a fundamental error the notion that experienced pain correlates exactly with the amount of nerve-ending stimulation.¹² She cited Wilbert Evans Fordyce (1923–2009), who developed the idea of operant conditioning as a factor in chronic pain and who championed cognitive

behavioral therapy strategies and behavioral principles for encouraging patients to become active again and to cut back on pain medication. The roots of pain, both Beecher and Fordyce theorized, are created by past experiences and may not be found in the body or explained by pathology.

Centers for Disease Control and Prevention figures reviewed by Dr. Ballantyne correlated the dramatic increase in opioid sales and overdose deaths with treatment between 1999 and 2010. Data from the Drug Abuse Warning Network show that, for every U.S. opioid overdose death in 2009 (n = 15,597), there were nine treatment-abuse admissions, 30 emergency department visits for misuse or abuse, 118 people with abuse/dependence issues, and 795 nonmedical users of opioids. Behind the dramatic increases, she explained, were the palliative care physician and pharmaceutical industry promotion of opioids for chronic pain, U.S. health care system factors, and U.S. cultural factors. The industry-funded "educational" messages at work, according to Dr. Ballantyne, were:

- Physicians are allowing patients to suffer needlessly because of "opiophobia."
- Opioid addiction is rare in pain patients.
- Opioids can be discontinued easily.
- Opioids are safe and effective in chronic pain.
- Palliative care principles (such as titration-to-effect) apply equally to chronic pain.^{13–16}

What's wrong with long-term continuous opioid use, Dr. Ballantyne said, is that it is based on a misunderstanding of chronic pain, specifically because suffering is related less to pain intensity than it is to meaning, disability, role, function, attitude, and expectation—all of which can be changed. Physiologically, she added, opioid use "commandeers the endogenous opioid system," leading to neuroadaptations linked to tolerance and dependence. "Giving exogenous opioids overwhelms these natural systems and prevents the protective defensive mechanisms from taking place ... Isolation, withdrawal, distress, family, job, culture, all influence the development of chronic pain and are indicators of derangement in natural opioid systems," she said.

The rate at which susceptible individuals will become addicted is fairly constant at 12% to 20%, with close correlation between the opioid amount and addiction. Activity and exercise, which are therapeutic for many pain conditions (especially musculoskeletal pain), are suppressed by opioid use.

Dr. Ballantyne pointed out that the evidence from modern imaging, which enables viewing of most pathological causes of pain, shows that two individuals with the same pathology on an image may experience pain very differently. Pain may become the focus of a life of suffering in one, while for another, the physical pain is sublimated or even disappears.

"The overuse of opioids for chronic pain is a distinctly U.S. problem," Dr. Ballantyne said. For 90% of chronic pain, opioids have not proven helpful, she said, mentioning specifically axial low-back pain without a pathoanatomical diagnosis, fibromyalgia, and headache.¹⁷ "What is the U.S. going to do about it?" she asked, urging what amounts to a "cultural transformation," including the "demedicalization of the most common pain conditions." For example, when a patient presents with back pain, she said, the old pathway would begin with investiga-

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tion through imaging leading to intervention if possible (e.g., surgery, injections), mild analgesics, and then strong analgesics. The new pathway would begin with measurement (e.g., depression, anxiety, childhood trauma) and continue through a holistic approach to counseling, encouraging of self-help and activation, and ending with mild analgesics.

The *CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016* discourages the use of long-acting opioids, suggests dose limitations, recognizes “legacy patients” as a different category, and considers acute opioid use as a pathway to chronic use.¹⁸ Dr. Ballantyne listed older theories and matched them with replacement ones (in italics), based on new evidence:

- Opioids are a reasonable option if all other treatments have failed.
*People who have failed all other treatments tend to have a high-risk profile, making opioids a bad choice.*¹⁹
- Opioids rarely cause addiction if used to treat pain (5% incidence).
*Opioids cause problematic use in up to 30%, and addiction in up to 20%.*²⁰
- Provided cautions are used, most chronic opioid treatment is safe and effective.
*Risk mitigation strategies have not been shown to reduce adverse outcome, and 80% do not get good long-term efficacy.*²¹
- There is no ceiling dose.
*Copious evidence now links adverse outcomes to high doses.*²²
- Long-acting opioids provide consistent analgesia with less risk of addiction.
*Long-acting opioids are more likely to produce tolerance, leading to loss of efficacy and dose escalation without protecting from addiction.*²³

In 2015, Dr. Ballantyne and colleague Mark D. Sullivan, MD, wrote: “We propose that pain intensity is not the best measure of the success of chronic-pain treatment. When pain is chronic, its intensity isn’t a simple measure of something that can be easily fixed. Multiple measures of the complex causes and consequences of pain are needed to elucidate a person’s pain and inform multimodal treatment.”¹⁶

Strong reactions to Drs. Ballantyne and Sullivan’s statements were voiced quickly after that publication, with one expert characterizing their recommendations as “totally inappropriate” and calling for Dr. Ballantyne to resign her academic post. Ignoring the authors’ call for “multimodal treatment,” that article states: “Ballantyne and Sullivan offered no alternative ‘fixes’ for pain treatment, other than patients learning to live with pain and sitting down for a chat with their doctors.”²⁴

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