CLINICAL STUDY

Adjuvant Medications That Improve Survival after Locoregional Therapy

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ABSTRACT

Purpose: To determine if outpatient medications taken at the time of liver tumor embolization or ablation affect survival.

Materials and Methods: A retrospective review was done of 2,032 liver tumor embolization, radioembolization, and ablation procedures performed in 1,092 patients from June 2009 to April 2016. Pathology, hepatocellular carcinoma (HCC) stage (American Joint Committee on Cancer), neuroendocrine tumor (NET) grade, initial locoregional therapy, overall survival after initial locoregional therapy, Child-Pugh score, Eastern Cooperative Oncology Group performance status, Charlson Comorbidity Index, and outpatient medications taken at the time of locoregional therapy were analyzed for each patient. Kaplan-Meier survival curves were calculated for patients taking 29 medications or medication classes (including prescription and nonprescription medications) for reasons unrelated to their primary cancer diagnosis. Kaplan-Meier curves were compared using the log-rank test.

Results: For patients with HCC initially treated with embolization (n = 304 patients), the following medications were associated with improved survival when taken at the time of embolization: beta-blockers ($P = .0007$), aspirin ($P = .0008$) and other nonsteroidal antiinflammatory drugs ($P = .009$), proton pump inhibitors ($P = .004$), and antivirals for hepatitis B or C ($P = .01$). For colorectal liver metastases initially treated with ablation (n = 172 patients), beta-blockers were associated with improved survival when taken at the time of ablation ($P = .02$).

Conclusions: Aspirin and beta-blockers are associated with significantly improved survival when taken at the time of embolization for HCC. Aspirin was not associated with survival differences after locoregional therapy for NET or colorectal liver metastases, suggesting an HCC-specific effect.

ABBREVIATIONS

COX = cyclooxygenase, ECOG = Eastern Cooperative Oncology Group, HCC = hepatocellular carcinoma, NET = neuroendocrine tumor, NSAID = nonsteroidal antiinflammatory drug, TAE = transarterial embolization

Locoregional therapies for liver tumors—thermal ablation, embolization, and radioembolization—trigger a cascade of downstream effects that can affect local recurrence as well as growth of distant tumors. After thermal ablation, immune cells infiltrate the ablation zone, which can result in either an antitumor immune response or immune tolerance for tumor antigens (1). Growth factors released after liver ablation can cause progression of tumors outside the ablation zone (2). After transarterial embolization (TAE), tumor ischemia stimulates angiogenesis and growth of the residual viable tumor (3,4). Embolization can also induce an antitumor immune response: for example, by increasing alpha fetoprotein–specific $CD4^+$ T cells after embolization of hepatocellular carcinoma (HCC) (5) or by decreasing regulatory T cells (6).

These downstream effects can be modulated by oral medications, which can thus affect outcomes after

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locoregional therapy. A randomized trial showed that oral ginsenoside Rg3, a ginseng extract with antiinflammatory and antiangiogenic effects, improved survival after transarterial chemoembolization of HCC (7). Sorafenib, an oral antiangiogenesis agent, may improve survival after transarterial chemoembolization of advanced HCC (4,8). Bumetanide, a diuretic that also inhibits glycolysis, increased tumor necrosis after TAE of HCC an animal model (9). Celecoxib, an antiinflammatory agent (cyclooxygenase [COX]-2 inhibitor), reduced distant tumor growth after liver ablation in an animal model (10).

The goal of this study was to find medications that improve survival after liver-directed locoregional therapy. This study examined outpatient medications (including both prescription and nonprescription medications) patients were taking for reasons unrelated to their primary cancer diagnosis. All of these medications are approved by the US Food and Drug Administration and have known safety profiles. Many of these medications have known effects on inflammation, angiogenesis, blood flow, or glucose metabolism and thus might have a synergistic effect with locoregional therapy (**Table 1**).

MATERIALS AND METHODS

This retrospective study was compliant with the Health Insurance Portability and Accountability Act and approved by the institutional review board. All liver tumor embolization, radioembolization, and ablation procedures performed from June 2009 to April 2016 (2,032 procedures in 1,092 patients) were reviewed. There were no exclusion criteria.

The most common pathologies were HCC (30%), colorectal liver metastases (23%), and neuroendocrine tumor

Table 1. Outpatient Medications and Medication Classes

Drug or Drug Category	No. Patients	Most Common Examples (Most to Least Common)	Mechanism*
Statin	97	Atorvastatin, simvastatin, rosuvastatin	I G A
Beta-blocker	156	Metoprolol, carvedilol, atenolol, nadolol	B
CCB	108	Amlodipine, diltiazem	B
ACE inhibitor/ARB	144	Lisinopril, losartan, valsartan, olmesartan	B
Diuretic	138	Hydrochlorothiazide, furosemide, spironolactone, triamterene	G B
Anticoagulant	80	Enoxaparin, rivaroxaban, warfarin	I R
Antiplatelet	121	Aspirin, clopidogrel	I
Aspirin	116		I G A R
NSAID (excluding aspirin)	106	Ibuprofen, naproxen, celecoxib	I G A R
Corticosteroids	68	Prednisone, dexamethasone, methylprednisolone	I G A R
Noncorticosteroid immunosuppressant	20	Everolimus, sirolimus	I
G-CSF	21	Pegfilgrastim, filgrastim	I
Antiviral (anti–hepatitis B, C)	26	Sofosbuvir, ledipasvir	I
Antiviral (not anti–hepatitis B, C)	28	Valacyclovir, acyclovir	I
Any antiviral	51	Sofosbuvir, ledipasvir, tenofovir, valacyclovir	I
Any antibiotic	127	Metronidazole, ciprofloxacin, sulfamethoxazole-trimethoprim, levofloxacin	I R
Metformin	52		I G A
Nonmetformin oral antidiabetic agents	55	Sitagliptin, glimepiride, glyburide	G
Insulin	59		G A
PPI	287	Pantoprazole, omeprazole, esomeprazole, lansoprazole	
Gabapentin	29		
Ursodiol	43		I R
Levothyroxine	58		
Iron	33		I A
Omega-3 polyunsaturated fatty acids	29		I A
Folic acid	21		I A
Cyanocobalamin	32		I
Vitamin C	33		I G A R
Vitamin D	139		I A

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; G-CSF = granulocyte colony-stimulating factor; NSAID = nonsteroidal antiinflammatory drug; PPI = proton pump inhibitor.
*A = angiogenesis; B = blood flow; G = glucose metabolism; I = immune response; R = radiation damage.