EVIDENCE-BASED REVIEW

Mechanism of Action, Pharmacokinetics, Efficacy, and Safety of Transarterial Therapies Using Ethiodized Oil: Preclinical Review in Liver Cancer Models

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ABSTRACT

Purpose: To systematically review mechanism of action, pharmacokinetics (PKs), efficacy, and safety of ethiodized oil–based locoregional therapy (LRT) for liver cancer in preclinical models.

Materials and Methods: A MEDLINE search was performed from 1988 to 2016. Search terms included hepatocellular carcinoma (HCC), HCC, liver-cell carcinoma, liver, hepatic, hepatocarcinoma, transarterial or chemoembolization, TACE, animal, Lipiodol, Ethiodol, iodized oil, and/or poppy-seed oil. Inclusion criteria were: publication in a peer-reviewed journal, an accepted animal model, and PK/safety/efficacy data reported. Exclusion criteria were: inadequate PK, safety, or efficacy data; anticancer drug name/dose not available; and article not in English. Outcomes included intratumoral anticancer drug uptake, PKs, tolerance, tumor response, and survival.

Results: Of 102 identified articles, 49 (49%) met the inclusion criteria. Seventeen, 35, and 2 articles used rat, rabbit, and pig models. Mechanism of action was investigated in 11 articles. Eleven articles reported drug uptake, PK, and tolerance data, showing 0.5%–9.5% of injected chemotherapy dose in tumor. Tumor-to-liver drug distribution ratios were 2–157. Toxicology data across 6 articles showed transient liver laboratory level elevations 1 day after LRT. There was no noteworthy liver or extrahepatic histologic damage. Nine articles reported tumor response, with 0%–30% viable tumor and –10% to –38% tumor growth at 7 days after LRT. Two articles reported survival, showing significantly longer survival after LRT vs untreated controls (56/60 d vs 33/28 d). Several articles described ethiodized oil mixed with radiopharmaceutical (n = 7), antiangiogenic (n = 6), gene (n = 6), nanoembolic (n = 5), immune (n = 2), or other novel (n = 1) agents.

Conclusions: Animal studies show preferential tumor uptake of anticancer agent, good hepatic/systemic tolerance, high tumor response, and enhanced survival after ethiodized oil–based LRT.

ABBREVIATIONS

DEE = drug-eluting embolic, FdUrd-C8 = 3′,5′-dioctanoyl-5-fluoro-2′-deoxyuridine, HCC = hepatocellular carcinoma, IL = interleukin, LRT = locoregional therapy, MN-16ET = N-[2-(triphenylmethyl)thioethyl]-3-aza-19-ethyloxycarbonyl-3-[2-(triphenylmethyl) thioethyl]octadecanoate, ODN = oligodeoxynucleotide, PK = pharmacokinetic, pMNC = porous magnetic nanocluster, siRNA = small interfering RNA, TNF = tumor necrosis factor, VEGF = vascular endothelial growth factor

Conventional transarterial chemoembolization refers to infusion of chemotherapeutic agents as an emulsion with ethiodized oil (Lipiodol Ultra-Fluid; Guerbet, Villepinte, France) followed by embolization with particulate agents (1). During conventional chemoembolization, ethiodized oil serves to emulsify and carry chemotherapeutic agents to tumor (2), facilitate intracellular drug entry (3), and embolize tumor microcirculation (4). Since the first reports of ethiodized oil chemoembolization in the early 1990s, the clinical benefit of conventional chemoembolization has been widely validated in medical practice (5). Nonetheless, the broadening focus of cancer therapeutic agents on minimally invasive, locoregional, and targeted treatments, as well as

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clinical advances in conventional chemoembolization, have spurred preclinical research to explore the mechanism of action of ethiodized oil as a drug delivery system and to discover new anticancer agent and ethiodized oil formulations. Such preclinical studies rely heavily on predictive animal cancer models to allow clinical translation for liver cancer treatment.

A comprehensive understanding of the available mechanistic, pharmacokinetic (PK), efficacy, and safety data of the reported ethiodized oil–based transarterial therapies in the treatment of liver cancer in animal models is therefore vital for the development of new human trials. This study was therefore undertaken to systematically review the available literature on the mechanism of action, PKs, efficacy, and safety of ethiodized oil-based locoregional therapies (LRTs) of liver cancer in preclinical models.

MATERIALS AND METHODS

Data Sources and Selection Process

A literature search was performed by a single reviewer (S.B.) using the MEDLINE database spanning the period from 1988 to 2016. The abstracts of identified publications were screened by two reviewers (S.B. and R.C.G.) for possible inclusion based on specific eligibility criteria, which were cooperatively developed by all authors. Eligible articles were reviewed in full by all authors and assessed for inclusion. Interreviewer discrepancies were resolved through consensus discussion. References within studies that met selection criteria were searched for other potentially relevant studies.

Search Terms

The following search terms—jointly conceived by all authors—were used to identify potential articles: "hepatocellular carcinoma" or "liver-cell carcinoma" and "transarterial chemoembolization" or "chemoembolization" or "intra-arterial injection" or "transarterial injection" or "hepatic artery injection" and "cell line model" or "mice model" or "rat model" or "rabbit model" or "pig model." All search terms were also combined with "Lipiodol," "Lipiodol Ultra-Fluid," "Ethiodol," "iodized oil," and "poppy-seed oil."

Inclusion and Exclusion Criteria

English language studies published in peer-reviewed journals that reported PK parameters (plasma anticancer drug level, drug tumor uptake, drug tumor-to-liver ratio), efficacy (tumor response, survival), or safety (serum hepatic marker level, liver histologic examination) data of ethiodized oil–based LRT in accepted animal models with liver cancer were included. Exclusion criteria included ethiodized oil suspension (given the lack of correspondence to clinical conventional chemoembolization), inadequate safety or efficacy data, anticancer drug name and/or dose not available, mouse model (not widely accepted), and article not published in English.

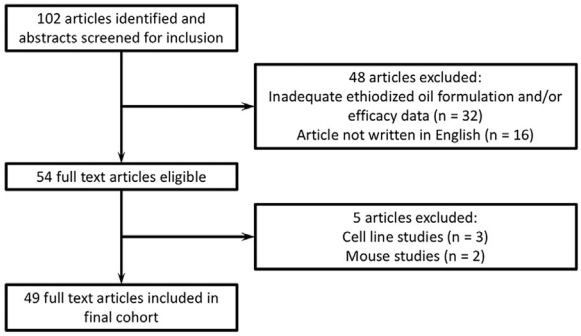

Figure 1. Flow chart delineating manuscript identification.

Outcome Measures

Data were compiled, and relevant outcomes—including intratumoral anticancer drug uptake, PK data, tolerance, tumor response, and survival—were tabulated on a per-study basis. Studies reporting outcomes of conventional chemoembolization with standard therapeutic agents (eg, doxorubicin) were reported distinctly from those that employed innovative agents.

RESULTS

Literature Search Results

Literature search yielded a total of 102 articles. Of these, 49 (48%) met inclusion criteria (2,4,6–52), of which 17 (35%), 35 (71%), and 2 (4%) articles used rat, rabbit, and pig models (some articles used more than one animal species). A flow chart of manuscript identification is presented in **Figure 1**. The included studies investigated mechanism of action (n = 11; 23%), ethiodized oil/chemotherapy PKs and efficacy (n = 16; 33%), ethiodized oil/chemotherapy safety (n = 6; 13%), therapeutic radionuclide administration (n = 7; 15%), antiangiogenic agent delivery (n = 6; 13%), gene therapy (n = 6; 13%), nanoembolization (n = 5; 10%), immunoembolization (n = 2; 4%), and novel chemotherapy agent LRT (n = 1; 2%).

Mechanism of Action

Ethiodized oil–mediated drug delivery.—The intravascular distribution of ethiodized oil after intra-arterial infusion was described in a rabbit model by de Baere et al in 1995 (6): oil droplets showed a propensity to pass through the largest arteries (diameter 30× larger than oil droplets) at a bifurcation, without passage into smaller vessels. Within 12–18 seconds after infusion, fourth- or fifth-order bifurcations were reached by intact, elongated oil droplets to penetrate terminal arterioles and microcapillaries (6,7). This selectivity accounted for the tendency of ethiodized oil droplets to preferentially "select" larger tumor neovasculature.

When ethiodized oil was injected into the hepatic artery in rat, rabbit, and swine, oil phase also dose-dependently appeared in the terminal portal venules (2,4,7–9) (**Fig 2**). Histologic and in vivo microscopy examinations of livers