



LIPIODOL[®] ULTRA FLUID

Ethyl ester of iodized fatty acids of poppy seed oil

Treatment of Liver Tumors with LIPIODOL[®] TACE: Technical Recommendations from Experts Opinion

**Thierry de Baere, Yasuaki Arai, Riccardo Lencioni,
Jean-François Geschwind, William Rilling, Riad Salem,
Osamu Matsui, Michael C. Soulen**

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Objective



A worldwide panel of experts participated in a consensus meeting to develop an internationally validated recommendation to standardize the **LIPIODOL®** TACE procedure.



Methods




The experts panel described: the patient selection, the pre-treatment imaging, the patient preparation, the intra-procedure imaging, the drugs, **LIPIODOL®** and embolic, the catheter positioning, the embolization technique and endpoint, the treatment schedule, the post-treatment care and imaging follow-up.




“These recommendations have been generated to encourage treatment standardization”


Patient selection

-  “Patient selection for TACE should include a comprehensive clinical assessment with particular attention to underlying liver disease and performance status. Laboratory assessment including liver function tests, complete blood count, renal function evaluation, and coagulation profile are important to determine whether **LIPIODOL®** TACE is the recommended treatment for patient. [...]”


Pre-treatment imaging

-  “A multiphasic computed tomography (CT) or dynamic contrast-enhanced magnetic resonance imaging (MRI) of the liver must be obtained for review by the multidisciplinary tumor board responsible for the clinical management of the patient. The images must not be older than 8 weeks and preferably within 4 weeks of the planned TACE procedure [...].”

Patient preparation

-  “Prior to the procedure patients are instructed to fast for 4-6 h. Antiemetic prophylaxis should be given and may vary but often include a 5-HT3 antagonist (e.g., ondansetron), intravenous steroids, and diphenhydramine. Antibiotic prophylaxis is inconsistently practiced without evidence-based data in the general population. [...]”

Intraprocedural imaging

-  “Excellent quality imaging during the procedure is critical to optimize guidance and appropriate targeting of the tumor. Thus, the use of 3D-angiography obtained with a rotational flat panel detector system (cone-beam CT) or combined MDCT-angiography system is recommended, if available. [...]”






“Patient selection for TACE should include a comprehensive clinical assessment with particular attention to underlying liver disease and performance status”


Drugs, LIPIODOL[®], and embolic

- “For HCC, the most common single anticancer drugs used during TACE are the anthracycline group including doxorubicin or epirubicin. [...]”
- “Several combination drug regimens have been reported the most popular being cisplatin, doxorubicin, and mitomycin C. [...]”
- “The drug(s) selected for TACE are mixed with **LIPIODOL[®]** to form an emulsion. Water-in-oil emulsion (droplets of the internal phase containing drug in aqueous solution and continuous external phase of oily **LIPIODOL[®]**) was demonstrated to be more densely retained within the tumors than the alternative oil-in-water emulsion.”
- “Contrast medium can be used for preparation of doxorubicin aqueous solution.”
- “In order to favor a water-in-oil emulsion, the volume of drug aqueous solution should be lower than the volume of **LIPIODOL[®]**, ideally one volume of drug to two volume of **LIPIODOL[®]** [...]”
- “The content of the syringe loaded with the drug should be first pushed towards the syringe containing Lipiodol, in order to favor a water-in-oil emulsion by inducing large drops of drug within **LIPIODOL[®]**.”
- “Vigorous mixing of the chemotherapy aqueous solution and **LIPIODOL[®]** via the 3-way stopcock generates sufficient energy to decrease the size of the internal phase droplets. At least 20 pumping exchanges through the stopcock are needed to obtain an internal phase size of droplets in the range of 70–100 microns. [...]”
- “The mixture must be prepared at the time of administration and must be used promptly after preparation. If necessary during the treatment session, the mixture can be re-homogenized.”
- “It is recommended to use a volume of **LIPIODOL[®]** equal or less to 15 ml in adults per session.”
- “The embolization component of TACE procedure, is used after injection of the drug/**LIPIODOL[®]** mixture.”
- “Gelatine sponge particles are the most commonly used particulate material. Gelatin sponge demonstrates complete recanalization in 1–2 weeks, therefore allowing for subsequent TACE treatment through the same tumor feeders.”

- **1 volume of drug to 2 volume of LIPIODOL[®]**
- **Push first the syringe loaded with the drug towards the syringe containing LIPIODOL[®]**
- **Vigorous mixing via a 3-way stopcock with at least 20 pumping exchanges**

Catheter positioning, embolization technique, and endpoint

-  "Superselective embolization is recommended when a single tumor or low number of tumors are treated, because such superselective placement allows for chemoembolization segmentectomy which has demonstrated better results than lobar or whole liver TACE. [...]"
-  "A major advantage of **LIPIODOL®** TACE is the ability to control the delivery of the treatment by continuous visualization of the therapeutic agents due to the radio-opacity of **LIPIODOL®**."
-  "**LIPIODOL®** drug emulsion is actively monitored until the tumor vascular bed is saturated, and stasis is obtained in the very peripheral branches."
-  "Gelfoam embolization performed after drug/**LIPIODOL®** emulsion delivery should induce complete stasis up to the catheter tip when placed superselectively."
-  "Due to the radio-opacity of **LIPIODOL®**, there is a real-time visualization of targeting and distribution of the chemotherapy, including visualization of non-target deposition, which is currently not possible with any other liver-directed therapies."



"Due to the radio-opacity of **LIPIODOL®,
there is a real-time visualization of targeting
and distribution of the chemotherapy"**

Treatment Schedule

- "At least two TACE procedures should be performed before treatment is abandoned due to lack of response. Indeed, 44–65 % of patients who were not initial responders to the first cycle of TACE demonstrated a significant response after the second session of treatment."
- "TACE sessions are performed 2–8 weeks apart according to treatment tolerance, treatment efficacy and the need for a subsequent treatment, until complete response is obtained."

Post-treatment Care and Imaging Follow-Up

- "Post-embolization syndrome is an expected toxicity of TACE and it is not regarded as a complication. Pain medication, antibiotic prophylaxis, antiemetic therapy, and gastric protection should be provided according to standard institutional protocols."
- "Evaluation of response relies on the assessment of tumor devascularization using mRECIST criteria that have been demonstrated as predictive of survival."
- "When using CT for evaluation, both non-enhancing area and area of iodized oil retention should be considered as necrosis and it was demonstrated by pathologic correlation in clinical setting."
- "The absence of Lipiodol deposition in a targeted area suggests that tumor feeders may have been missed, usually from watershed territories within the liver or from extrahepatic collaterals. It is advisable to consider targeting the remaining untreated tumor with a new session of TACE before the patient has been declared progressive and TACE is discontinued."

- **At least 2 TACE procedures should be performed before treatment is abandoned in case of lack of response**
- **Both non-enhancing area and area of Lipiodol retention should be considered as necrosis treatment is abandoned in case of lack of response**



LIPIODOL® ULTRA-FLUID. Composition: Ethyl esters of iodized fatty acids of poppy seed oil 10 mL, corresponding to an iodine content of 480 mg/mL. **Indications(* *):** In diagnostic radiology - Hysterosalpingography - Ascending urethrography – Lymphography – Sialography - Fistulography and exploration of abscesses - Exploration of frontal sinuses - Pre and post-operative cholangiography. In interventional radiology – Visualisation and localization (by selective intra-arterial use during CT) of liver lesions in adults with known or suspected hepatocellular carcinoma - Visualisation, localisation and vectorisation during Trans-Arterial Chemo-Embolisation (TACE) of hepatocellular carcinoma at intermediate stage, in adults – Selective embolization in combination with Histoacryl glue (particularly for arteriovenous malformation or aneurysms) – Selective injections of LIPIODOL ULTRA-FLUID into the hepatic artery for diagnostic purposes where a spiral CT scan is not practical. In endocrinology - Prevention of severe cases of iodine deficiency. **Posology and method of administration (*):** have to be adapted according to the type of examination, the territories explored, the age and weight of the patient. The volume to be administered depends on the particular requirements of the technique and the size of the patient. **Contraindications:** Hypersensitivity to LIPIODOL ULTRA-FLUID - Confirmed hyperthyroidism - Patients with traumatic injuries, recent haemorrhage or bleeding – Hysterosalpingography during pregnancy or acute pelvic inflammation – Bronchography. In interventional radiology (Trans-Arterial Chemo-Embolization), Administration in liver areas with dilated bile ducts unless drainage has been performed. **Special warnings and special precautions for use(*):** There is a risk of hypersensitivity regardless of the dose administered. Lymphography: Pulmonary embolism may occur immediately or after few hours to days from inadvertent systemic vascular injection or intravasation of LIPIODOL ULTRA-FLUID: Perform radiological monitoring during LIPIODOL ULTRA-FLUID injection and avoid use in patients with severely impaired lung function, cardiorespiratory failure or right-sided cardiac overload. Hypersensitivity: all iodinated contrast agents can lead to minor or major hypersensitivity reactions, which can be life-threatening. These hypersensitivity reactions are of an allergic nature (known as anaphylactic reactions if they are serious) or a non-allergic nature. They can be immediate (occurring within 60 min) or delayed (not occurring until up to 7 days later). Anaphylactic reactions are immediate and can be fatal. They are dose-independent, can occur right from the first administration of the product, and are often unpredictable: avoid use in patients with a history of sensitivity to other iodinated contrast agents, bronchial asthma or allergic disorders because of an increased risk of a hypersensitivity reaction to LIPIODOL ULTRA-FLUID. Thyroid: can cause hyperthyroidism in predisposed patients. Lymphography saturates the thyroid with iodine for several months and thyroid exploration should be performed before radiological examination. Chemo-Embolization: Trans-Arterial Chemo-Embolisation is not recommended in patients with decompensated liver cirrhosis (Child-Pugh ≥ 8), advanced liver dysfunction, macroscopic invasion and/or extra-hepatic spread of the tumour. Renal insufficiency must be prevented by correct rehydration before and after the procedure. Oesophageal varices must be carefully monitored. Hepatic intra-arterial treatment can progressively cause an irreversible liver insufficiency in patients with serious liver malfunction and/or undergoing close multiple sessions. The risk of superinfection in the treated area is normally prevented by administration of antibiotics. Embolization with glue: An early polymerisation reaction may exceptionally occur between LIPIODOL ULTRA-FLUID and certain surgical glues, or even certain batches of glue. Before using new batches of LIPIODOL ULTRA-FLUID or surgical glue, the compatibility of LIPIODOL ULTRA-FLUID and the glue must be tested in vitro. **Interaction with other medicinal products and other forms of interaction (*):** Metformin, Beta blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin-receptor antagonists, Diuretics, Interleukin II. **Fertility, pregnancy and lactation (*):** LIPIODOL ULTRA-FLUID must only be used in pregnant women if absolutely necessary and under strict medical supervision. Breastfeeding should be discontinued if LIPIODOL ULTRA-FLUID must be used - **Effects on ability to drive and use machines:** The effects on ability to drive and to use machines have not been investigated - **Undesirable effects(*)** most adverse effects are dose-related and dosage should therefore be kept as low as possible :hypersensitivity, anaphylactic reaction, anaphylactoid reaction, vomiting, diarrhea, nausea, fever, pain, dyspnea, cough, hypothyroidism, hyperthyroidism, thyroiditis, pulmonary embolism, cerebral embolism, retinal vein thrombosis, lymphoedema aggravation, hepatic vein thrombosis, granuloma. **Overdose (*)** The total dose of LIPIODOL ULTRA-FLUID administered must not exceed 20 mL - **Pharmacodynamic properties (*)** Pharmacotherapeutic group: X-ray contrast media, iodinated; ATC code: V08A D01. Water-insoluble iodinated contrast medium. **Presentation (**)** - 10 mL glass ampoule, box of 1 - 10 mL glass ampoule, box of 50. **Marketing authorization holder (*)**: Guerbet - BP 57400 - F-95943 Roissy CdG cedex – FRANCE. Information: tel : 33 (0) 1 45 91 50 00. Revision: September 2, 2015.

(*) For complete information please refer to the local Summary of Product Characteristics.

(**) Indications, volumes and presentations may differ from country to country.

Reporting of suspected adverse reactions is important as it helps to continuously assess the benefit-risk balance. Therefore, Guerbet encourages you to report any adverse reactions to your health authorities or to your local Guerbet representative.

Countries in which cTACE indication is registered : France, Japan, South Korea, Austria, Peru, Turkey, Hungary, Czech Republic, Mongolia, Argentina, The Netherlands, Vietnam, Thailand, Mexico, Taiwan & Brazil.

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Conclusion

«These recommendations have been generated to encourage treatment standardization. These recommendations may be used as general guide for LIPIODOL® TACE [..]. However, the interventional radiologist treating the patient is ultimately responsible for treatment approach given the unique complexity of patient and tumor characteristics. [..]. Patients will be best served when the treating interventional Oncologist is taking an active role in patient selection, treatment allocation, and postprocedure care.»