UPMC
STARZL TRANSPLANTATION INSTITUTE
LIVER TRANSPLANT POLICIES AND PROCEDURES

POLICY LT-ICC-0619
LIVER TRANSPLANTATION IN PATIENTS WITH INTRAHEPATIC CHOLANGIOCARCINOMA OR MIXED CHOLANGIO/HEPATOCELLULAR CARCINOMA

PURPOSE

This policy is intended to guide the management of liver transplant candidates with intrahepatic cholangiocarcinoma (ICC) or mixed cholangio/hepatocellular (ICC/HCC) carcinoma.

BACKGROUND

Incidence of Cholangiocarcinoma

- 1-2/100,000 for all cases of cholangiocarcinoma
  - 60-70% at hepatic duct bifurcation (Klatskin tumors)
  - 20-30% distal common bile duct
  - 5-10% peripheral, arising from intrahepatic ducts
- 3% of all gastrointestinal cancer diagnoses worldwide are chalongiocarcinomas
- 15% of all liver cancers
  - Intrahepatic 2,600 cases/yr.
  - Extrahepatic 3,000 cases/yr.
- the incidence of ICC has been increasing worldwide over the past 4 decades.

Cholangiocarcinoma (CCA) at one point was regarded as a contraindication to orthotopic liver transplantation (OLT). Protocols for pre-transplant chemoradiation combined with careful screening have shown acceptable long-term survival in patients with hilar cholangiocarcinoma (See Protocol: UPMC LT-CCA).

Recent data from protocols utilizing systemic chemotherapy with a mandatory observation period, followed by exploration, then liver transplantation, has shown a significant 5-year survival advantage over other therapies[1].

INCLUSION and EXCLUSION CRITERIA

A. Inclusion Criteria
- otherwise appropriate transplant candidate
- peripheral ICC or ICC/HCC
- dx of CCA based on a hypervascular lesion on CT or MRI with at least *one* of the following:

a. Biopsy consistent with cholangiocarcinoma
b. Carbohydrate antigen 19-9 greater than 100 U/ml

- no limit to tumor size or number of tumors if all intrahepatic
- no evidence of extrahepatic disease by contrast CT or MRI abdomen/pelvis, non-contrast chest CT, and/or PET CT C/A/P

B. Exclusion Criteria

- extrahepatic disease, including LN involvement
- otherwise unacceptable candidate for liver transplantation based on medical, surgical, or psychosocial criteria

UNOS REQUIREMENTS FOR LISTING PATIENTS WITH CHOLANGIOCARCINOMA

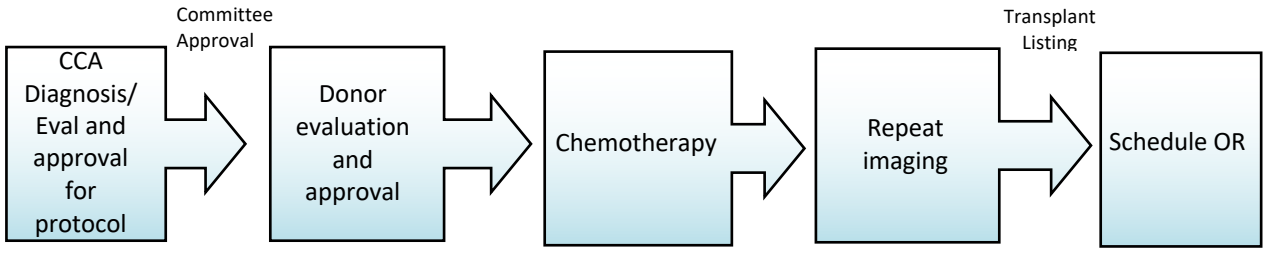
Patients with intrahepatic, non-hilar cholangiocarcinoma do not meet requirements of OPTN policy (See 9.6.A) to receive MELD exception points. Patients may be able to receive a deceased-donor transplant but would need to receive that allocation based on native MELD. It is unlikely that a patient with adequate liver function to allow the required chemotherapy would have a MELD score high enough to be allocated a deceased-donor liver. Additionally, the transplant team would be cautious to start chemotherapy in a patient without a living-donor option due to the very low chance of transplantation. For this reason, patients ideally would have a living-donor option prior to entrance into the protocol.

STAGING

Standard liver transplant evaluation protocol (including non-contrast CT chest and Abdomen/pelvis MRI) plus:

CT/PET
Ca19-9

TREATMENT PROTOCOL OVERVIEW



TREATMENT PROTOCOL

A. *Neoadjuvant Chemotherapy*

Gemcitabine 1000mg/m^2 and Cisplatin 25 mg/m^2 on days 1 and 8 of every 21 days for 6 months. *(ref. N Engl J Med 2010; 362:1273-81.)*

B. Locoregional Therapy

Patients may benefit from locoregional therapy as a bridge to transplant. For smaller tumors (< 3 cm), consider percutaneous radiofrequency ablation, preferable at time of initial biopsy. For larger tumors or tumors inaccessible by RFA, consider transarterial chemoembolization (Gem/Cis or Gem/Oxaliplatin based). For centrally located tumors, consider external beam radiation. *(ref HepatoBiliary Surg Nutr 2017;6(2):105-116.)*

C. *Exploratory Laparotomy (at time of scheduled living-donor recipient procedure)*

1. Staging laparotomy in recipient, prior to living-donor being taken into OR
    - Thorough abdominal exploration
    - Biopsy any suspicious lesions for frozen analysis
    - Biopsy choledocal and hepatic arterial node for frozen analysis
    - Examine caudate to determine whether caval-sparing OLT possible
    - Resect >0.5 cm segment bile duct to rule out extension. This is done to ensure there was no underlying, undiagnosed hilar CCA. If positive, consider Whipple procedure.

2. Extrahepatic metastases, LN metastases or local extension of disease to adjacent organs or tissues precludes transplantation

D. *While on treatment* protocol, the patient will receive:

1. Abd MRI and non-contrast chest CT at 3 months. If no evidence of extrahepatic disease, continue chemotherapy for full duration of protocol. If evidence of extrahepatic disease is found, the patient is removed from the protocol and deemed not-a candidate for transplant. Equivocal findings may require further work-up for confirmation or the patient may be continued for full protocol treatment and proceed to exploration (at the discretion of the team).
2. Repeat PET CT C/A/P at 6 months to evaluate for extrahepatic disease which may preclude transplant or may direct the pre-transplant exploration.
3. CA19-9 at 3 months and 6 months to serve as baseline trend markers.

POST-TRANSPLANT CHEMOTHERAPY

Post-transplant, patients will be maintained on Capecitabine (Xeloda) 1000 mg/m^2 bid for 14 days of every 21 days for 6 months as tolerated based on symptoms or lab data suggestive of toxicity.

Other notable things about Xeloda (capecitabine)

1. Dosage adjustment for moderate renal impairment (crcl 30-50ml/min) – use 75% of starting dose; contraindicated for CrCl <30ml/min
2. Hematologic adverse effects 3.2%, 1.7%, 2.4% grade 3-4 neutropenia, thrombocytopenia, or decreased Hgb respectively – manageable from my perspective
3. Diarrhea and dehydration are major concerns, especially as precipitators of AKI
4. Drug Drug Interactions – no pharmacokinetic interactions with tac, CSA, EVR, SIR, but I would not be surprised if TAC levels increase in the face of drug induced diarrhea; no PK interactions with azathioprine or mycophenolic acid derivatives

REFERENCES

1. Lunsford, KE. Sustained Biologic Response to Neoadjuvant Therapy Predicts Excellent Liver Transplant Outcomes for Locally Advanced Intrahepatic Cholangiocarcinoma. ATC abstract and oral presentation, 2019.
2. *Koay EJ et al.* Management of unresectable intrahepatic cholangiocarcinoma: how do we decide among the various liver-directed treatments*? HepatoBiliary Surg Nutr* 2017;6(2):105-116
3. Khan SA, et al. Cholangiocarcinoma. 2005 *Lancet* Vol 366;1303-1314.
4. Valle J, et al. Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer *N Engl J Med* 2010; 362:1273-81.
5. Lunsford KE, et al. Propensity-Matched Analysis of Patients with Mixed Hepatocellular Cholangiocarcinoma and Hepatocellular Carcinoma Undergoing. *Liver Transplantation 24 1384–1397.*