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Insights on liver transplantation and multimodal treatment for intrahepatic cholangiocarcinoma

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Abstract

The treatment of intrahepatic cholangiocarcinoma (iCCA) has traditionally been limited to surgical resection or systemic therapy. The role of liver transplantation in the management of iCCA is a topic currently being explored. This paper serves as a review to highlight past, present, and future work being done in regard to liver transplantation for iCCA. Strict protocols with specific selection criteria have shown promising results. Neoadjuvant therapy, locoregional therapy, and immunotherapy are some of the tools that may aid in bridging selected patients with iCCA to liver transplantation. There are currently three ongoing trials designed to further evaluate the efficacy of liver transplantation for iCCA. As criteria continue to be refined and evidence accumulates, liver transplantation may become a suitable option as a curative treatment strategy for highly selected patients with unresectable intraoperative cholangiocarcinoma.

Keywords: Intrahepatic cholangiocarcinoma, liver transplantation, transplant oncology

INTRODUCTION

Intrahepatic cholangiocarcinoma (iCCA) is a rare primary liver tumor that arises from the cholangiocytes in the bile ducts proximal to the hepatic duct bifurcation. The incidence of iCCA and extrahepatic cholangiocarcinomas has increased based on data collected over the last 20 years[1]. Risk factors for the

development of iCCA include intrahepatic lithiasis, primary sclerosing cholangitis, toxic exposure, parasite infection, chronic liver disease, and metabolic abnormalities; however, a large portion of iCCAs arise without an identifiable trigger[2,3]. iCCA often presents with non-specific symptoms and is most commonly found on imaging in asymptomatic patients being worked up for abnormal liver enzymes or unrelated issues[4].

Currently, surgical resection of iCCA remains the only modality for curative intent treatment; however, an R0 resection is only possible in 30%-40% of all patients with iCCA owing largely to advanced disease at the time of diagnosis[4,5]. Contraindications to resection include invasion or encasement of major vasculature, intrahepatic or extrahepatic metastases, or nodal metastasis identified on diagnostic staging studies[6]. With the intent to cure resection, overall survival (OS) and disease-free survival (DFS) at 5 years remains poor. OS at 5 years was 30% to 35% and the median aggregate OS was about 28 months despite the majority of cases achieving an R0 resection[7]. A retrospective study by Hyder *et al.* found that DFS was 32.1% at 5 years with a median recurrence-free survival (RSF) of 20.2 months, noting major vascular invasion, tumor size, and nodal metastases as predictors for increased recurrence risk[8]. Liver transplantation for iCCA may be efficacious for properly selected patients after recent studies have shown promising results. We sought to review the current literature to provide a review that highlighted liver transplantation in the setting of iCCA as well as adjunct therapies and current ongoing studies.

NEOADJUVANT TREATMENT

Neoadjuvant therapy for iCCA with the intent to bridge to liver transplantation includes several different approaches including systemic chemotherapy and locoregional approaches. These approaches intend to downstage disease in order to meet the eligibility criteria for transplant. For chemotherapy, a gemcitabine-cisplatin regimen is most commonly employed. Locoregional therapies include transarterial chemotherapy (TACE) and radioembolization with yttrium-90 (Y90). Based on the ABC-02 Phase III trial, gemcitabine-based therapy with the addition of cisplatin was associated with a significant survival advantage for biliary tract cancers compared to gemcitabine alone[9]. A recent case report in 2016 showed the successful use of Y-90 radioembolization in conjunction with systemic chemotherapy to bridge a patient with a large, unresectable iCCA to liver transplantation (LT) with DFS noted at 3 years of follow-up[10].

ROLE OF IMMUNOTHERAPY

Reports of immunogenic features of biliary tract cancers have suggested checkpoint inhibition may result in antitumor immune responses[11]. The TOPAZ-1 trial (NCT03875235) is the first global phase 3 study to evaluate first-line immunotherapy and gemcitabine-cisplatin in unresectable, locally advanced, recurrent or metastatic biliary tract cancers. Patients were randomized in a 1:1 fashion to receive durvalumab plus gemcitabine cisplatin or placebo plus gemcitabine-cisplatin until disease progression or unacceptable toxicity. The primary outcome of this study was OS and results showed that durvalumab plus gemcitabine-cisplatin significantly improved OS as well as progression-free survival compared to placebo plus gemcitabine-cisplatin[12]. Given increasing work in the field of molecular targets in biliary tract cancers, specifically targeted fusion genes including FGFR2, HER2, MSI-H and NTRK, there is increasing interest in the utility of pemigatinib in intrahepatic cholangiocarcinoma[11]. The utility of immunotherapy and targeted agents continues to evolve; however, its utility in the context of liver transplantation is yet to be studied and analyzed.

LIVER TRANSPLANTATION FOR INTRAHEPATIC CHOLANGIOCARCINOMA

Due to poor overall survival and high early recurrence rates, LT for iCCA has traditionally been a contraindication[13,14]. However, more recent studies have illuminated prognostic risk factors aiding in the

selection of acceptable candidates for LT with similar OS[15,16]. A retrospective study by Sapisochin *et al.* in 2016 found that patients with "very early" (< 2 cm iCCA) found at pathologic examination of explanted livers could achieve acceptable 5-year survival and low recurrence rates with LT[15]. As demonstrated by the Mayo Clinic protocol for LT in the setting of hilar cholangiocarcinoma, strict patient selection coupled with neoadjuvant therapy and preoperative staging has made LT a viable option that was once deemed a contraindication[17]. For the purposes of this discussion, we will limit our scope to iCCA and not mixed-type tumors and those that are found post explant.

Only a few prospective trials utilizing LT as a treatment modality for unresectable, locally advanced iCCA have been completed. An early prospective case series study was able to demonstrate promising recurrence-free survival and overall survival for patients that received LT for locally advanced iCCA when selected based on pre-transplant disease stability[18]. Results from a case series study demonstrated by McMillan *et al.* were able to demonstrate a 1-, 3-, and 5-year survival of 100%, 71%, and 57%, respectively, with the development of a strict protocol that utilized neoadjuvant therapy coupled with ongoing monitoring to select candidates with favorable tumor biology for LT. Key inclusion criteria: diagnosis confirmed with percutaneous biopsy, solitary tumor ≥ 2 cm in diameter or multiple tumors. Key exclusion criteria: distant or lymph node metastases, encasement or involvement of major vascular structures. Those deemed unresectable progressed to LT evaluation. Prior to listing for LT, patients had to demonstrate diseases stability (tumor number and size) on cross-sectional imaging for at least 6 months while on neoadjuvant systemic chemotherapy (the majority received gemcitabine-based therapy with cisplatin) and liver-directed therapy in the form of locoregional therapy and external beam radiation. A staging laparotomy was performed prior to LT to evaluate for extrahepatic disease not detected on cross-sectional imaging. A total of 18 out of the 37 patients listed for LT underwent LT and were monitored closely with repeat imaging and CA-19-9 for at least 5 years. Of the 19 patients who did not undergo transplant, 5 were able to undergo resection after Neoadjuvant therapy (NAT), 3 developed extrahepatic disease, 2 died from disease, 2 had aborted transplants, and 7 remained listed. Recurrence-free survival at 1 and 3 years was 70% and 52%, respectively, with a median recurrence time of 11 months. They were able to demonstrate that the use of disease response to neoadjuvant therapy allowed for an appropriate selection of candidates that achieved reasonable survival and DFS[16]. Another large series from UCLA sought to retrospectively evaluate the outcomes of 31 patients with intrahepatic cholangiocarcinoma. Of the 31, 14 patients had cirrhosis, and 11 received NAT. The majority of patients had tumors > 5 cm and 5-year survival was reported to be 56% for patients with tumors > 5 cm and 38% for patients with tumors < 5 cm, although this difference did not reach statistical significance. Moreover, neoadjuvant chemotherapy or local therapy alone did not show a superior statistical significance compared to no neoadjuvant treatment but combining neoadjuvant treatment modalities resulted in better survival outcomes.[19].

The Mayo Clinic mirrors a similar protocol for the management of biopsy-proven unresectable iCCA with LT. Key inclusion criteria: single lesion ≤ 3 cm in diameter, no vascular invasion or extrahepatic disease, no prior attempt at surgical resection, no microvascular or poorly differentiated histology, and reasonable LT candidate. Those that qualify undergo a pre-transplant evaluation that includes: MRI/MRCP, CT-abdomen with contrast, CT-chest without contrast, CA 19-9, EUS with sampling of celiac and hilar nodes, and PET scan in addition to standard evaluation. Prior to listing, patients undergo radiofrequency ablation (RFA) of the lesion and are then monitored with cross-sectional imaging every 3 months for a total of 6 months. If there is no evidence of tumor recurrence at the RFA site or any new lesions at 6 months, then the patient is listed for liver transplantation. Should a recurrence occur, re-ablation may be needed and the monitoring for recurrence resets at the time of re-ablation. While listed, the patients are monitored at 3-month time intervals with a CA 19-9 and cross-sectional imaging of the chest and abdomen. Post-transplant, patients

are monitored at 4 months and annually for 4 years with a CA 19-9 and cross-sectional imaging of the chest and abdomen[20]. For patients who are unable to go downstaging due to underlying cirrhosis and with early-stage disease, upfront transplantation may provide a possible treatment avenue. Per current NCCN guidelines, after resection imaging is the only recommended modality for surveillance per current guidelines[21]. CA 19-9 New avenues of detection are currently underway, with methods such as circulating tumor DNA (ctDNA) showing promise for surveillance[22].

ONGOING CLINICAL TRIALS FOR LT WITH ICCA

Currently, there are three ongoing clinical trials evaluating LT for unresectable, early, stable, and advanced iCCA.

Liver Transplantation for Non-Resectable Intrahepatic Cholangiocarcinoma: a Prospective Exploratory Trial (TESLA Trial - NCT04556214).

Single-group, open-label study currently in the enrollment phase with plans for 15 participants. Based in Oslo University Hospital (Oslo, Norway) with the primary outcome of overall survival from screening. Secondary outcomes include OS from the time of relapse and DFS. Key inclusion criteria include: histologically verified diagnosis of iCCA, first-time iCCA or liver-only recurrence after previous liver resection for iCCA, unresectable, no vascular invasion, no extrahepatic disease or lymph node metastases on imaging, good performance status, and receiving at least 6 months of chemotherapy or locoregional therapy. The estimated completion date is May 2035[23].

Liver Transplantation for the Treatment of Early Stages of Intrahepatic Cholangiocarcinoma in Cirrhotics (NCT02878473).

Single-group, open-label study currently in the enrollment phase with plans for 30 participants. Based on the University Health Network (Toronto, Canada) with the primary outcome of 5-year patient survival and secondary outcome of 5-year cumulative risk of recurrence after LT. Key inclusion criteria: liver cirrhosis of any etiology, biopsy-proven iCCA ≤ 2 cm, unresectable disease, no vascular or biliary or extrahepatic disease on preoperative imaging. The estimated completion date is January 2029[24].

Liver Transplant for Stable, Advanced Intrahepatic Cholangiocarcinoma (NCT04195503).

Single-group, open-label study currently in the enrollment phase with plans for 10 participants. Based on the University Health Network (Toronto, Canada) with the primary outcome of 5-year patient survival and secondary outcomes of 5-year DFS and 1-year patient survival. Key inclusion criteria include: histologically proven diagnosis of iCCA, unresectable, no vascular or extrahepatic or lymph node involvement on preoperative imaging, disease stability ≥ 6 months on gemcitabine-based therapy or, if progresses to second-line therapy, then must be stable for ≥ 6 months on that regimen, and suitable living donor. The estimated completion date is December 2031[25].

CONCLUSION

Intrahepatic cholangiocarcinoma has traditionally been associated with a dismal prognosis, especially in unresectable diseases with a low chance of downstaging to progress to an intent to cure resection. The re-emergence of LT for iCCA in select candidates offers a new treatment modality to improve OS and DFS. As demonstrated by recent studies, strict selection criteria for LT are crucial to ensure optimal oncological

outcomes to justify the utilization of organs. Neoadjuvant therapy in the form of systemic chemotherapy, transarterial radioembolization, and transarterial chemoembolization coupled with tumor behavior and dynamic screening have shown potential in the advancement of treatment for iCCA. Further investigations regarding prognostic risk factors associated with iCCA and the effects neoadjuvant therapies have will help further refine selection criteria in order to select appropriate candidates for liver transplantation. Immunotherapy may emerge as a key tool, but its utility in the context of LT has yet to be evaluated. Several clinical trials investigating the efficacy of LT for iCCA are currently ongoing and will provide invaluable information in the near future.

DECLARATIONS

Authors' contributions

Manuscript conception and design: Yohanathan L
collection, interpretation and analysis: Logarajah S, Nida J, Simoneau E, Yohanathan L
Draft manuscript preparation: Logarajah S, Nida J, Yohanathan L
Manuscript review: Logarajah S, Nida J, Simoneau E, Yohanathan L

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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