

Medical therapies for intra-hepatic cholangiocarcinoma

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Background

Cholangiocarcinoma (CCA) is a heterogeneous group of cancers arising from the biliary tree. Intrahepatic CCA (iCCA) arise from biliary ducts within the hepatic parenchyma, anatomically above second-order bile ducts[1], and have been increasing in global incidence over the last few decades. Less than 30% of patients with CCA have resectable disease at diagnosis and most patients require systemic therapy. Advancements in understanding the diverse genetic and molecular signatures of CCA has identified novel targets for cancer specific therapy.

Systemic Chemotherapy

Post surgical resection, the BILCAP study demonstrated adjuvant therapy with capecitabine improves relapse-free and overall survival[2]. In the palliative setting, systemic chemotherapy with gemcitabine and cisplatin remains standard first-line therapy, with a progression free survival (PFS) of 11.7 months demonstrated[3]. FOLFOX (folinic acid, 5-FU and oxaliplatin) is second-line therapy, demonstrating an increase in 12 month survival, though only modest increases in median survival[4].

Targeted Cancer Therapy

iCCA carcinogenesis arises from an interplay of extracellular bile acids, growth factors and cytokines causing aberrant activation of cholangiocyte cell surface receptors. Deregulation of downstream intracellular signalling lead to genetic and epigenetic alterations, driving changes to cell proliferation, survival and migration/invasion. Multiple gene mutations have been identified and histological subtypes of iCCAs show distinct molecular profiles. Large-duct iCCA arising from peribiliary glands exhibit KRAS and TP53 gene mutations, whereas small-duct iCCA are characterised by mutations in isocitrate dehydrogenase (IDH) and fibroblast growth factor receptor 2 (FGFR2) gene fusions. Based on liquid or tissue-based biopsy DNA profiling, it is estimated at least 20-30% of advanced CCAs have somatic alterations targetable for novel therapies.

FGFR Antagonists

Fibroblast growth factor (FGF) signalling has a role in cell development and angiogenesis, with aberrant FGF receptor activation implicated in carcinogenesis. FGFR2 gene fusion with gene partners, most frequently BICC1, is highly enriched in iCCA. FGFR1-3 inhibitor Pemigatinib is the first FDA approved targeted agent for treatment of iCCA, with 82% of patients with FGF2 gene alterations responding to therapy in the FIGHT-202 trial[5]. A multi-centre randomised open-label study trialling first-line pemigatinib versus gemcitabine/cisplatin underway. Further oral FGFR antagonists including infigratinib, derazantinib and futibatinib show promising disease control responses in phase II trials.

IDH Antagonists

IDH gene mutations lead to accumulation of pro-oncological metabolite 2-hydroxyglutarate, driving DNA hypermethylation. IDH1/2 mutations are found in 10-20% of iCCAs and inhibitors including ivosidenib (IDH1), AG221 (IDH2) and AG881 (pan-IDH1/2) have shown promising clinical results. Ivosidenib demonstrated an increase in PFS of 2.7 compared to 1.4 months with placebo in a phase III study[6].

Further targeted therapy

HER2 overexpression is seen in 5% of iCCAs, with combination trastuzumab and pertuzumab inhibition demonstrating response[7]. Novel inhibitors, zanidalamab (HER2) and neratinib (pan-HER), have shown promising preliminary results. Mutations in the RAS-MAPK signalling pathway are implicated in multiple cancers and a basket study showed 47% of BRAF^{V600E}-mutated iCCA patients responded to combination BRAF/MEK inhibition[8]. A randomised phase II trial of patients failing to respond to first-line chemotherapy showed protein kinase inhibition with regorafenib significantly improved PFS compared to placebo[9]. Preliminary results of two phase I/II trials evaluating arginase (INCB001158) and casein-kinase 2 (simitasertib) inhibitors in combination with first-line gemcitabine/cisplatin demonstrate promising response rates and tolerability, with full results awaited.

Immunotherapy

There is limited data for the role of immunotherapy in iCCA. A basket study showed mismatch repair-deficient iCCAs showed a 17% response to pembrolizumab[10], with future studies assessing immunotherapy in combination with other systemic therapies.

Future Directions

The advent of tissue subtyping of iCCAs has increased potential targets for medical therapy. Current trials such as the SAFIR ABC-10 study will use molecular subtyping to deliver precision medicine and identify therapies to improve survival in advanced disease.

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