Hepatology Snapshot:

Medical therapies for intrahepatic cholangiocarcinoma

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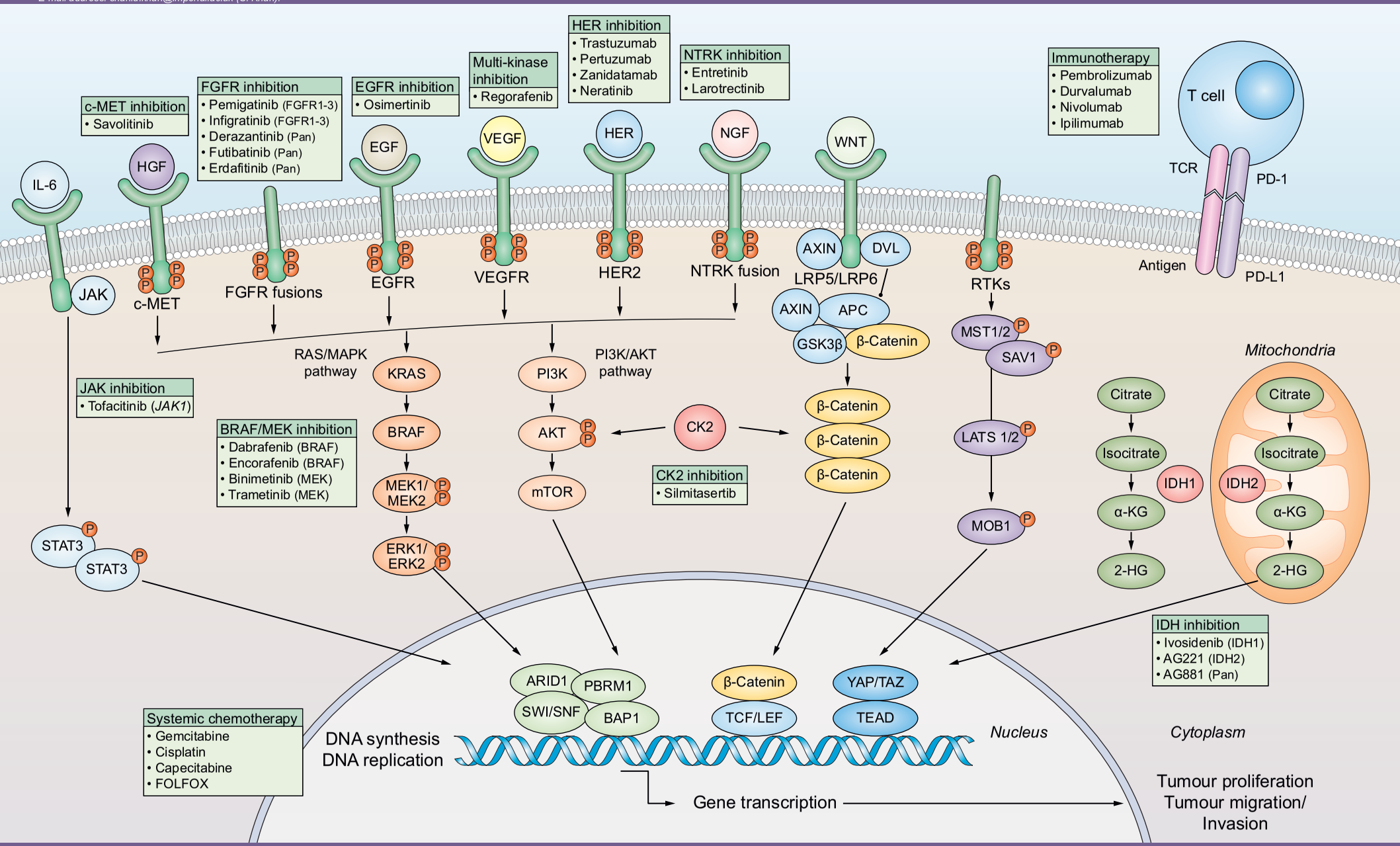

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Background

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 iCCAs are resectable at diagnosis and most patients require systemic therapy. Advances in understanding the diverse genetic and molecular signatures of CCA have identified novel targets for cancer-specific therapy.

Systemic chemotherapy

Post surgical resection, the BILCAP study demonstrated adjuvant capecitabine chemotherapy significantly improved overall survival (OS) to 53 months compared to 36 months in the non-treatment group.[2] In the palliative setting, combination gemcitabine/cisplatin therapy remains first-line therapy, with a significantly improved OS of 11.7 months and progression-free survival (PFS) of 8.0 months compared to gemcitabine monotherapy.[3] Following progression after first-line therapy, FOLFOX-treated patients demonstrated 25.9% survival at 12 months, with a median OS of 6.2 months, and it is the recommended second-line therapy.[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. Multiple gene mutations have been identified. Large-duct iCCAs arising from peribiliary glands often exhibit *KRAS* and *TP53* gene mutations, whereas a subset of small-duct iCCAs are characterised by mutations in isocitrate dehydrogensase (*IDH*) and fibroblast growth factor receptor 2 (*FGFR2*) gene fusions. Based on DNA profiling of liquid or tissue-based biopsy samples, an estimated 20-30% of advanced CCAs have somatic alterations that are targetable with novel therapies. To date, only 1 phase III study for targeted therapy is available, with most studies focusing on patients progressing after first-line therapy.

FGFR antagonists

FGF signalling has a role in cell development and angiogenesis. *FGFR2* gene fusion with gene partners, most frequently BICC1, is prevalent in 15-20% of iCCAs. The 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 *vs*. gemcitabine/cisplatin is underway. Further, oral FGFR antagonists including infigratinib, derazantinib and futibatinib have shown promising disease control responses in phase II trials.

IDH antagonists

IDH gene mutations lead to accumulation of pro-oncological metabolite 2-hydroxyglutarate. 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. In IDH1-mutant iCCAs with progression on previous therapy, 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/pertuzumab inhibition leading to responses.[7] Novel inhibitors, zanidalamab (HER2) and neratinib (pan-HER), have shown promising preliminary results. A basket study showed 47% of $BRAF^{V600E}$-mutated iCCA patients responded to combination BRAF/MEK inhibition.[8] Neurotrophic tyrosine kinase receptor inhibition has been investigated in iCCAs and a randomised phase II trial of patients failing to respond to first-line chemotherapy showed protein kinase inhibition with regorafenib significantly improving PFS compared to placebo.[9] Preliminary results of phase I/II trials evaluating arginase (INCB001158) and casein-kinase 2 (silmitasertib) inhibitors in combination with first-line gemcitabine/cisplatin have demonstrated promising response rates and tolerability, with full results awaited.

Immunotherapy

There is limited data on the role of immunotherapy in iCCA. Mismatch repair-deficient iCCAs showed a 17% response to pembrolizumab,[10] with future studies assessing immunotherapy in combination with 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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Conflict of interest

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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

SK and JB conceived the article structure; MV drafted the manuscript. All authors reviewed and approved the final version of the manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.04.004.

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