ASCO update: hepatocellular and cholangiocellular carcinoma

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Summary At ASCO 2022 several studies were presented. This short review is about hepatocellular carcinoma, and cholangiocellular carcinoma and trials like STAMP, ImmunoTACE trial, FOENIX-CCA2, ImmunoTACE trial, for example.

Keywords Hepatocellular carcinoma · Cholangiocarcinoma · STAMP · ImmunoTACE trial · FOENIX-CCA2

ASCO 2022: cholangiocarcinoma and hepatocellular carcinoma

Cholangiocarcinoma (CC) is a malignant tumor arising from the epithelium of the bile ducts. CC accounts for only about 3% of all gastrointestinal tumors but this cancer is the second most common primary liver tumor. Over 90% of these tumors are adenocarcinomas [1]. Depending on the anatomical location, CC is divided into intrahepatic cholangiocarcinoma (iCC), perihilar cholangiocarcinoma (pCC), and distal cholangiocarcinoma (dCC). pCC and dCC are also defined as extrahepatic cholangiocarcinoma. pCC is the most common type of CC, accounting for 50–60% of cases. In general, the incidence of all forms of CC seems to be increasing [2]. Currently, the prognosis of CC is poor due to the difficult of early diagnosis and limited treatment methods, where patients associate with a median survival of 24 months after initial diagnosis. Several risk factors have been identified: primary sclerosing cholangitis (PSC), bile duct cysts, parasitic infections (mainly in Asia), hepatolithiasis, toxins, HBV (Hepatitis B) and HCV (Hepatitis C) infection. Moreover, some evidence has indicated that potential risk factors include also alcohol consumption, smoking, diabetes, NASH (non-alcoholic liver disease), inflammatory bowel disease, and genetic polymorphisms. However, over 70% of patients are diagnosed as CC without any predisposing factors [3]. According to current evidence, surgical resection is the only curative treatment method that is approved by all guidelines. In very selected cases, liver transplant can be offered to cure the patient. Unfortunately, there is a high relapse rate in the minority of patients who undergo potentially curative surgery [4], which is the reason why there is a high clinical need for adjuvant therapy. However, several adjuvant therapy strategies failed to show a benefit versus surveillance [5]. I would like to briefly remind the readers of the dates of the BiCap. A total of 447 patients with biliary tract cancer (BCT) were randomized to capecitabine (n=223) or observation (n=224). Sensitivity analyses by intention-to-treat were adjusted to nodal status, grade of disease, and gender (447 patients). This trial demonstrated benefit from capecitabine in terms of overall survival (OS; hazard ratio [HR] 0.71, 95% confidence interval [CI] 0.55–0.92; P<0.01; median OS 51 months [95% CI 35–59] and 36 months [95% CI 30–45] for capecitabine and observation arms, respectively). There was also benefit from adjuvant capecitabine in terms of relapse-free survival (median 25 months [95% CI 19–37] and 18 months [95% CI 13–28] for capecitabine and observation arms, respectively). Based on these results, adjuvant capecitabine is at the moment standard of care following surgery for biliary tract cancer.

At this year’s ASCO a multicenter, open-label, randomized, phase II trial called STAMP was presented. The Korean colleagues investigated the role of gemcitabine/cisplatin (Gem/Cis) in patients with at least...
one regional lymph nodes metastasis (N1 or greater), complete macroscopic (R0 or R1) and extrahepatic cholangiocarcinoma cancer—a group, which has a very poor prognosis. Patients with distant metastasis or R2 disease, previous chemotherapy or radiotherapy, or a serum CA 19-9 level ≥ 100 U/mL were excluded. Here is should be emphasized again that half of the patients had perihilar cancer, while the other half distal cholangiocarcinoma. Patients were randomized 1:1 to Gem/Cis (gemcitabine 1000 mg/m² IV (intravenously), and cisplatin 25 mg/m² IV on day 1 and 8, every 3 weeks)—the protocol we use as first-line therapy in the metastatic setting or capecitabine (CAP; 1250 mg/m² orally twice daily on days 1–14, every 3 weeks) for 8 cycles. Primary endpoint was disease-free survival (DFS), secondary endpoints were overall survival (OS) and safety. A total of 101 patients (50 for Gem/Cis group and 51 for CAP group) were included in the intention-to-treat population. Perihilar and distal bile duct were primary tumor sites in 45 patients (44.6%) and 56 patients (55.4%), respectively, and 32 patients (31.7%) had R1 resection. Patient characteristics were well balanced between the two arms. With a quite long median follow-up duration of 28.7 months (interquartile range [IQR] 17.2–39.4), the 2-year DFS rates were 38.5% (1-sided 90% CI 29.5–47.4%) in Gem/Cis group and 25.1% (17.2–39.4), the 2-year DFS rates were 38.5% (1-sided 90% CI 29.5–47.4%) in Gem/Cis group and of course hand–foot skin reaction (HR = 36, 72.0%) in the CAP group. The median DFS were 14.3 months (10.7–16.5 months) in Gem/Cis group and 11.1 months (8.4–12.7 months) in CAP group (HR = 0.96 [0.71–1.30], p = 0.86). The median OS were 35.7 months (29.5 months–not estimated [NE]) in Gem/Cis group and 35.7 months (30.9 months–NE) in CAP group (HR = 1.08 [0.72–1.64], p = 0.81). But if you look at the grade 3–4 adverse events (AEs), these occurred in 42 patients (84.0%) and 8 (16.0%) in Gem/Cis and CAP groups, respectively. The most common AE of grade 3–4 was neutropenia (n = 36, 72.0%) in the Gem/Cis group and of course hand–foot skin reaction (n = 4, 8.0%) in the CAP group.

If you look carefully at the subgroup analyzes of the DFS and OS, you will see that the results do not favor any particular regiment. The authors concluded that Gem/Cis is feasible but failed to improve survival outcomes compared to CAP.

Conclusion: capecitabine still remains the standard therapy in the adjuvant setting for resected BTC. Hopefully soon, we see the results of the ATICCA trial, which is another adjuvant trial. And we will learn more about the role of gemcitabine/cisplatin versus capecitabine.

Around 60 to 70% of patients will be diagnosed with advanced disease, which is defined as inoperable or metastatic disease. For these patients, palliative treatment, usually in the form of systemic chemotherapy, is the only treatment option. Unfortunately, survival outcome is historically poor in this patient group.

In patients with advanced/metastatic intrahepatic CCA median overall survival (mOS) time is approximately 1 year with first-line gemcitabine/cisplatin and approximately 6 months with second-line chemotherapy (either FOLFOX or Nal-IRI/-5FU).

In recent years, however, we have learned that cholangiocarcinoma is a model for precision medicine in the gastrointestinal tract.

For instance, we learned in the past, FGFR2 fusions occur in 10–20% of patients with iCC.

FOENIX-CCA2 is a study of futibatinib, an oral highly selective, irreversible FGFR1–4 inhibitor. Futibatinib binds to the ATP-binding pocket of FGFR1–4 resulting in the inhibition of FGFR-mediated signal transduction pathways. This leads to reduced tumor cell proliferation and increased tumor cell death in tumors with FGFR1–4 genetic aberrations.

FOENIX-CCA2 was a single-arm phase 2 study that enrolled patients with advanced/metastatic iCCA with FGFR2 fusion/rearrangement and progressive disease (PD) after ≥ 1 prior treatment (including gemcitabine plus platinum-based chemotherapy). Patients received futibatinib 20 mg once daily until PD/intolerability. The primary endpoint was objective response rate (ORR) per RECIST v1.1 by independent central review. Secondary endpoints were DOR (Duration of Response), disease control rate (DCR), progression-free survival (PFS), OS, safety, and patient-reported outcomes.

This medication demonstrated efficacy with durable responses in patients with iCCA harboring FGFR2 fusion/rearrangements in the pivotal FOENIX-CCA2 phase 2 study. At the primary analysis of this trial (data cutoff: October 1, 2020), an objective response rate (ORR) of 41.7% was observed, with a median duration of response (mDOR) of 9.7 months. At ASCO 2022, the group reported updated efficacy (including mature OS data) and safety data from the final analysis with an additional 8 months of follow-up.

At the time of the final data cutoff median follow-up was 25.0 months, and 96/103 patients (93%) had discontinued therapy. The median number of therapy cycles was 13.0 for a median therapy duration of 9.1 months. The confirmed ORR was 41.7% (43/103) and thereby the same as of the primary analysis, as was the DCR (at 82.5%). Fortunately, the ORR was consistent across all subgroups. The mDOR was 9.5 months, and 74% of responses lasted ≥ 6 months. mPFS was 8.9 months, with a 12-month PFS rate of 35.4%. mature mOS was 20.0 months, with a 12-month OS rate of 73.1%.

Furthermore, we have to be aware of the common therapy-related adverse events, which included hyperphosphatemia (85%), like all FGFR inhibitors, alopecia (33%), dry mouth (30%), diarrhea (28%), dry skin (27%), and fatigue (25%). These side effects resulted in discontinuation in 4 patients (4%). Quality of life was maintained from baseline to cycle 13. Nevertheless, findings from the final analysis of FOENIX-CCA2 confirm the results of the primary analysis and reinforce the durable efficacy and continued tolerabil-
ity of futibatinib in previously treated patients with advanced/metastatic iCCA harboring FGFR2 fusion/ rearrangements. Mature OS data were consistent with data from the primary analysis and far exceed historical data in this patient population.

What else was exciting: for the first time, during the session, the results of the exploratory biomarker analysis on circulating tumor DNA (ctDNA) for FGFR2 were reported. Ninety-two percent of the patients provided these data with 83% having FGFR2 fusions and rearrangements. This equated to 87% positive percentage agreement from baseline to ctDNA analysis for the tissue samples collected at both time points. Of course, more data are needed before we can use this tool in our daily clinical practice, but there is great potential especially in lack of tissue.

These results represent another example of promising precision medicine in ICC. At present, the phase 3 FOENIX-CCA3 trial (NCT 04093362) is evaluating futibatinib versus gemcitabine and cisplatin in the first line in patients with cholangiocarcinoma and FGFR2 rearrangements. We will certainly also see the actual data here soon.

Let’s go to the next interesting post—this is again about the topic of precision medicine. We know from case series and small clinical trials that about 5–20% of biliary tract cancer has a Her-2 mutation. In gallbladder cancer, the Her-2 positive rate is estimated to be 30% and in ICC only 5%. The authors were able to show in their preliminary study that Her-2 expression patterns in biliary tract cancer are more similar to those of gastric cancer than breast cancer, including heterogeneity. In the HERB trial, a Japanese multicenter, single-arm phase II trial, the investigator used Trastuzumab-deruxtecan (T-Dxd), an antibody-drug conjugate composed of a humanized monoclonal anti-HER2 antibody and a topoisomerase I inhibitor. This drug has already shown benefit in Her-2 positive breast and gastric cancer patients. In this trial patients with biliary tract cancer, who were refractory or intolerant to a gemcitabine containing regime were tested with biliary tract cancer, who were refractory or intolerant to a gemcitabine containing regime were tested for Her-2. Between March 2019 and March 2020, 300 patients were screened: 61 patients had Her-2 positive tumors. The Her-2 expression was centrally confirmed (Her-2-positive: IHC3+ or IHC2+/ISH+, and Her-2-low-expressing [Her2-low]: IHC/ISH status of 0/+, 1+/−, 1+/−, or 2+/−). After progression the patients received 5.4 mg/kg of T-Dxd every 3 weeks.

The primary endpoint was confirmed objective response rate (ORR) in HER2-positive patients by independent central reviewer. The secondary endpoints were defined as progression-free survival (PFS), overall survival (OS) and disease control rate (DCR) in Her-2-positive/-low patients. But also, the incidence of treatment-emergent adverse events (TEAEs) was assessed as secondary endpoints. In the trial a total of 32 patients—24 with Her2-positive and 8 with Her2-low BTCs—were included and received T-Dxd. Twenty-two patients were identified for primary efficacy analysis. Among the 22 patients IHC3+ and IHC2+/ISH+ were 45.5% and 54.5%. The primary site of the cancer was the gallbladder in 11 patients; 6 patients had an intrahepatic CC, 3 an intrahepatic and only 2 patients had an Ampulla vateri cancer. The patients’ baseline characteristics were well balanced.

The median number of prior regimens was 2 (range 1–4). The confirmed ORR in Her2-positive patients was 36.4% (8/22; 2 CR and 6 PR; 90% confidence interval [CI] 19.6–56.1), indicating statistically significant improvement in ORR (P = 0.01). The DCR, median (m) PFS, mOS were 81.8% (95% CI 59.7–94.8), 4.4 months (95% CI 2.8–8.3), 7.1 months (95% CI 4.7–14.6), respectively.

The common TEAEs were anemia (53.1%), neutropenia (31.3%), and leukopenia (31.3%). TEAEs leading to drug discontinuation occurred in 8 patients (25.0%). Eight patients (25.0%) had interstitial lung disease. In conclusion T-Dxd showed interesting and promising activity in patients with Her2-expressing BTCs, but also in Her-2 low expressing patients. Although the safety profile was generally consistent with other T-Dxd studies, ILD, an important identified risk of T-Dxd, requires more careful monitoring and intervention. However, an international multicentric phase 3 study is required to confirm these findings. However, we have another therapy option for these selected group of patients.

In summary at this ASCO 2022, there was exciting and groundbreaking data in the therapy of cholangiocarcinoma. We will be able to offer our patients some as a result.

**Hepatobiliary carcinoma**

Hepatobiliary carcinoma (HCC) is the third leading cause of cancer deaths worldwide, with a relative 5-year survival rate of approximately 18%. Over the last several decades the incidence of HCC has steadily risen and in the coming decades, this is anticipated to continue to increase [6].

The diagnosis of hepatocellular carcinoma peaks in people aged between 60 and 70 years, and predominantly affects men [7]. It is well known that the incidence varies by geographical region and ethnicity. Most of the patients have a background of chronic liver disease because of chronic infections with the hepatitis B virus (HBV) or hepatitis C virus (HCV), alcohol abuse or alcoholic steatohepatitis (ASH), and non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH). Although the prevalence of virally driven hepatocellular carcinoma has declined, the incidence of NAFLD and NASH-related liver cancer has increased [8]. In the future, we will need surveillance guidelines especially for this growing group of patients.

Treatment strategies are laid down in the various guidelines. However, the most commonly used guideline is the Barcelona Clinic of Liver Cancer (BCLC)
algorithm. It divides the patients into different treatment groups: very early stage (BCLC 0), early stage (BCLC A), intermediate stage (BCLC B), advanced stage (BCLC C), and terminal stage (BCLC D) [9].

Patients detected in a very early stage without vascular invasion or extrahepatic spread and also with preserved liver function can be managed according to the country-specific guidelines (= access to liver transplantation!) [9]. If liver transplantation is not possible, the first treatment approach is ablation.

In the intermediate stage, a therapy option is intraarterial therapy, because HCC is a well-vascularized tumor. This particular therapeutic strategy can be performed in a various number of ways: bland particle embolization (TAE), chemoembolization (conventional transarterial chemoembolization [cTACE] or drug-eluting bead [DEB]-TACE), or radioembolization. In all cases, the hepatic artery is accessed with microcatheters via groin access. In order to increase the effectiveness of TACE, several randomized trials have been conducted to evaluate TACE combinations.

At ASCO 2022, a randomized phase II clinical trial from England evaluated low-dose cyclophosphamide and TACE with or without vaccination with dendritic cells (DC) pulsed with HepG2 lysate ex vivo in patients with hepatocellular carcinoma. In a previous study of this group, they could demonstrate using autologous monocyte-derived DC pulsed ex vivo with HepG2 cell lysate showed some clinical benefit with evidence of antigen-specific T-cell responses in patients with advanced HCC. The current trial reports the activity of this vaccine in combination with TACE in patients with HCC.

All patients also received low-dose cyclophosphamide to deplete regulatory T cells and thereby enhance vaccination. Patients with intermediate stage HCC (performance status 0–2, Child Pugh A/B7) were randomized 1:1 to TACE plus low-dose cyclophosphamide (group 1) or TACE plus low-dose cyclophosphamide plus dendritic cell vaccination (group 2). Cyclophosphamide was administered on day 1 and 29 followed by TACE on day 31 (± DC infusion), with further cyclophosphamide on days 60, 90 and 120 (± additional DC infusions on days 62, 92 and 122).

The primary endpoint was progression free survival (PFS) by RECIST v1.1. Secondary endpoints included radiological response by RECIST v1.1, PFS and radiological response according to modified (m) RE-CIST, overall survival (OS), immune response and toxicity.

In all, 55 patients from 3 UK centers were randomized of whom 48 were evaluable (24 in each arm). Median PFS by RECIST criteria was significantly longer in group 2 compared to group 1 (18.6 vs 10.4 months: hazard ratio [HR] 0.43, 80% CI 0–0.59; one-sided p = 0.02). Median PFS using mRECIST criteria showed a similar magnitude of benefit (18.6 vs 10.8 months: HR 0.48, 95% CI 0.22–1.02). Median OS was 25.7 months in group 2 vs 21.5 months in group 1 (HR 0.61, 95% CI 0.27–1.38). Group 2 showed a higher overall response rate (complete and partial response) by RECIST (54% vs 29%) and mRECIST (75% vs 54%) and a higher disease control rate (complete and partial response and stable disease) by RECIST (92% vs 67%) and mRECIST (88% vs 67%).

Treatment with DC infusions was well tolerated; the most common adverse events were chills (30%), fatigue (22%) and nausea (22%), all of which were low grade. Immune response analyses are currently ongoing. The addition of tumor lysate-pulsed DC infusions to treatment with TACE plus low-dose cyclophosphamide significantly increased PFS in patients with HCC. Further investigation on the role of DC infusions in the treatment of HCC is warranted.

In summary it is certainly very exciting work, but the question is whether TACE really will play such a big role in our clinical routine in the future. One must not forget that every TACE can be accompanied by a deterioration in liver function. Also, we need to account for the current evolving immunotherapy landscape.

At ESMO 2022 and ASCO GI 2023, more exciting data regarding the HCC will certainly be presented.

Unfortunately, the majority of patients are detected in late stage. Most of the time, these patients need systemic treatment. In the last several months we have learned a lot about new phase III trial in HCC.

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