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Emerging facets in the treatment of patients with hepatopancreaticobiliary malignancies

Hepatocellular carcinoma (HCC) is diagnosed at an early stage in 30%-40% of patients[1]. Potentially curative treatments include surgical therapies such as resection and liver transplantation and locoregional procedures such as radiofrequency ablation[1]. Chemoembolisation is recommended for patients with preserved liver function and disease confined to the liver, generally without vascular invasion.[1] The 5-year survival rates of up to 60%-70% are achieved in well-selected patients. However, disease that is diagnosed at an advanced stage or with progression after locoregional therapy has a dismal prognosis, owing to the underlying liver disease and the lack of effective treatment options.[2,3] The oral multikinase inhibitor sorafenib is the only approved systemic therapy for the first-line treatment of advanced disease with a median survival of 10.7 months reported for those patients receiving sorafenib vs 7.9 months in those receiving placebo.[4] Recently, it has been reported that regorafenib provides survival benefit in patients with HCC who have progressed on sorafenib therapy.[5] The median survival was 10·6 months for regorafenib vs 7·8 months for placebo.[5]

The overall 5-year survival rate for patients with a diagnosis of pancreatic ductal adenocarcinoma (PDAC) is $<5\%$.[6] Only 20% of patients present with localized, nonmetastatic disease which is suitable for resection.[7] Those who undergo resection and receive adjuvant therapy with the gemcitabine/capecitabine combination have a median survival of 28 months and a 5-year survival of 28.8%.[8] More than half of patients with PDAC have disease considered locally advanced and unresectable, because of local invasion of adjacent structures, and these patients can be challenging to treat due to local tumor burden and associated complications such as pain, pancreatic insufficiency, biliary obstruction, and early satiety/gastric outlet obstruction.[9] Local control and quality of life are therefore important issues in this disease group. Existing systemic therapies are only modestly effective in patients with advanced disease, and the median survival for patients with metastatic disease who are fit for the chemotherapy regimen consisting of oxaliplatin, irinotecan, 5-fluorouracil, and leucovorin (FOLFIRINOX) is 11.1 months,[10] the nab-paclitaxel/gemcitabine combination; 8.5 months[11] and gemcitabine alone; 5.6 months.[12] The FOLFIRINOX and nab-paclitaxel/gemcitabine combinations have not been evaluated in randomised-controlled trials involving patients with locally advanced PDAC, but these combination regimens are used by many clinicians for the treatment of patients with locally advanced PDAC with a good performance status, with gemcitabine alone considered a better option for patients with a borderline performance status.[9]

Biliary tract cancers (BTCs) are an understudied and poorly understood collection of diseases, encompassing cancers of the extrahepatic and intrahepatic bile ducts and the gallbladder.[13] The only potentially curative options are complete surgical resection, resulting in 5-year survival

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rates of 8%-40%,[14] and liver transplantation, with 5-year survival rates of approximately 30%, or up to 71% with the addition of neoadjuvant therapy in a highly selected population able to complete therapy.[15-17] In the BILCAP randomized trial, patients with resected BTC were randomized to capecitabine postsurgery vs observation alone.[18] The intention to treat median relapse-free survival reported was 25 months (95% CI: 19-37) for the capecitabine arm, and 18 months (95% CI: 13-28) for the observation arm. The median intention to treat overall survival was 51 months (95% CI: 35-59) for the capecitabine arm and 36 months (95% CI: 30-45) for the observation arm (hazard ratio is 0.80 [95% CI: 0.63-1.04, $P = 0.097$]).[18]

The only phase III randomized clinical trial for patients with a diagnosis of metastatic BTC demonstrating a survival benefit was the Advanced Biliary Cancer 02 (ABC-02) trial, which demonstrated that the combination of cisplatin plus gemcitabine was superior to gemcitabine alone in progression-free (8.0 vs 5.0 months, respectively) and overall survival (11.7 vs 8.1 months, respectively).[19] There is emerging evidence suggesting differences in the tumor biology of BTC by anatomical subtype, with varying rates of driver genomic mutations identified, including *isocitrate dehydrogenase 1/2* (*IDH1/2*)[20] and *fibroblast growth factor receptor 2* (*FGFR2*) mutations.[21] However, the duration of response to FGFR inhibitors in intrahepatic cholangiocarcinoma, for example, can be limited in some patients, due to clinical acquired resistance,[22] and so a greater understanding of the underlying molecular pathophysiology of these clinical diseases is necessary to advance the development of effective therapeutic strategies.

However, a recently reported comprehensive genetic analysis of patients with PDAC,[23] reported that only 3 of 225 patients (1%) received a matched therapy based on sequencing results, and so the recommendation was to consider incorporation of routine germline genetic analysis and to encourage identification of DNA profiles that may predict for clinical benefit from agents that target DNA damage repair in patients with PDAC[24] and/or immunotherapy.[23]

The programmed death 1 (PD-1) pathway is upregulated in many tumors and in the surrounding microenvironment, and blockade of this pathway with antibodies to PD-1, or its ligands has led to clinical responses in patients with many different types of cancers, such as melanoma, non–small-cell lung cancer, and renal-cell carcinoma.[25,26] More recently, it has been reported that the PD-1 checkpoint inhibitor, nivolumab, had a manageable safety profile in patients with histologically confirmed HCC, with or without hepatitis B or C, whose disease had progressed while receiving at least 1 previous line of systemic therapy, including sorafenib, or who were intolerant of, or refused, sorafenib therapy.[27] The objective response rate, as assessed by response evaluation criteria in solid tumors version 1.1 (RECIST v1.1),[28] in patients treated with 3 mg/kg nivolumab in the dose-expansion phase was 20% and 15% in the dose-escalation phase, which compared favorably to the previously reported 2% response rate, as measured by RECIST, to first-line sorafenib in patients with advanced HCC.[4] Bang et al[29] have presented interim data of the biliary cohort of KEYNOTE-028, which is an on-going phase 1b trial of pembrolizumab monotherapy for patients with PD-L1-positive advanced tumors. Of the 89 patients with BTC screened for PD-L1 expression, 42% had PD-L1-positive tumors, and an overall response rate of 17% was reported, with all patients having received ≥1 prior therapy, including 38% who received ≥3 prior therapies.[29]

However, in 14 patients with PDAC, antibody-mediated blockade of PD-L1, in monotherapy, did not produce any responses in a phase 1 trial in patients with advanced cancers, including non–small-cell lung cancer, melanoma, colorectal cancer, renal-cell cancer, ovarian cancer, gastric cancer, and breast cancer.[25]

The integration of palliative care into standard oncology care is becoming increasingly recognized since the publication of a study by Temel et al,[30] where patients with newly diagnosed metastatic non–small-cell lung cancer were randomised to receive either early palliative care integrated with standard oncology care or standard oncology care alone. There were significant improvements in quality of life, mood and overall survival among patients receiving early palliative care (11.6 months vs 8.9 months, $P = 0.02$), and these patients received less aggressive end-of-life care.[30] The American Society of Clinical Oncology have now published evidence-based recommendations on the integration of palliative care into standard oncology