Editorial

Systemic treatment of biliary tract cancer: now we have evidence

The once-perceived barriers in developing an evidence base for the treatment of biliary tract cancers were numerous: the rarity of the disease, the frailty of the patient population, poor outcomes and the lack of coordinated research activity, to name but a few.

In 2019, these concerns have been proven to be unfounded. The incidence in Western populations is between 0.5 to 5/100,000/year, making biliary tract cancer uncommon rather than rare (https://www.cancerresearchuk.org/health-professional/cancer-statistics/). These patients are often unwell, but large interdisciplinary teams have optimised overall decision-making, enabling greater use of systemic therapy. [1] Long-term survival outcomes remain modest, but improving, and research activity, both academic and commercial, has never been greater.

Chemotherapy is the standard of care in the adjuvant and the advanced settings. Although the BCAT[2] (gemcitabine) and PRODIGE-12[3] (gemcitabine plus oxaliplatin) adjuvant studies were negative (arguably because they were small underpowered studies), BILCAP[4] has established capecitabine as adjuvant therapy, with a median survival of over 50 months. The advanced biliary tract cancer (ABC) studies, primarily ABC-02, [2-4] have established cisplatin and gemcitabine (CisGem) as standard first-line treatment. This is despite several challengers, [5-7] including the FUGA-BT study comparing CisGem to gemcitabine plus S-1, presented in this issue of *Annals*.[15] Second-line therapy has established FOLFOX as a standard of care, although the benefit was modest. [5] These studies are major achievements for ABC, an uncommon cancer; however, for all these advances, the median overall survival for advanced disease remains 12 months and must be improved.

The contribution of improved supportive care must be emphasised. The BILCAP study statistical analysis plan had to be modified twice because of the surprisingly good outcome for the surgery-only arm. [4] The active symptom control arm of the ABC-06 study [5] also performed better than expected, supporting the value of careful management of these often unwell patients, possibly done more carefully in trials than we are routinely offering in practice. Our therapies are only as good as our basic medical care.

The pursuit of actionable molecular alterations in oncology has been exciting. Originally dependent on opportunistic molecular profiling outcomes, [8] consistent driver alterations have been found in biliary tract cancer.[9-11] In particular, intrahepatic cholangiocarcinomas are likely to have significantly improved outcome for molecularly selected subgroups of ABC patients. Currently, only IDH1 inhibitors have tested positively in a prospective study (https://agiospharmaceuticalsinc.gcs-web.com/), but other promising studies are ongoing (NCT02052778; TAS-120, targeting FGF/FGFR) and it is possible that ABC will represent one of the malignancies most amenable to targeted therapy. [12] Importantly, these data will mandate tumour profiling for biliary tract cancers similar to that which has occurred for BRCA in adenocarcinoma of the pancreas, [6] potentially increasing therapeutic options for these cancers of high unmet need. Although actionable alterations may improve outcomes,

it currently leaves half of all ABC patients - commonly those with extrahepatic ABC - without a known actionable alteration.

The FUGA-BT study reported in this issue of *Annals* aimed to provide an alternative to CisGem with a combination of gemcitabine and S-1 (GemS1), an oral fluoropyrimidine combination consisting of tegafur, gimeracil, and oteracil. The study recruited 354 patients and found GemS1 to be both non-inferior to CisGem and well tolerated; the authors suggest that GemS1 should be a standard of care option. This study adds to the growing body of high-quality clinical trial level data of chemotherapy in ABC. Although the conclusion is not in doubt, I would hesitate to consider GemS1 a globally accepted standard of care for a number of reasons.

There are differences in the schedules for cisplatin and gemcitabine used in the FUGA-BT study and those used in the ABC studies. Unlike the ABC studies, gemcitabine in FUGA-BT was continued after cisplatin discontinuation and the cumulative dose of cisplatin was capped at 400mg/m^2. There were also the added toxicities of fluoropyrimidine therapy (diarrheoa, 20.9%; oral mucositis, 28.8%; rash, 23.7%), which many would consider significant. Most importantly, S1 is preferred in Japan over other more internationally accepted fluoropyrimidines, such as capecitabine or 5-FU. It has been proposed that the pharmacogenomics of the Japanese population confers a benefit, although the data in both Japanese and Western populations do not support this claim. [13,14] As long as this issue remains uncertain, it is unlikely that S1, and consequently GemS1 for ABC, will feature prominently in oncology practice outside of Japan.

Morizane and colleagues are nevertheless to be congratulated for performing an excellent randomised phase 3 study in ABC[15]. It is only with these well-conducted studies that we will overcome the historical prejudice that biliary tract cancers are untreatable. The continuing support from our excellent user organisations (www.ammf.org.uk; https://cholangiocarcinoma.org; https://www.cascap.in.th) increase the profile of these very needy patients. Biliary tract cancer has made it into the mainstream of modern oncologic practice, but there is much more to do.

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References

1. Khan SA, Davidson BR, Goldin RD, Heaton N, Karani J, Pereira SP. Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. Gut 2012;61.
2. Bridgewater J, Lopes A, Beare S, et al. A phase 1b study of Selumetinib in combination with Cisplatin and Gemcitabine in advanced or metastatic biliary tract cancer: the ABC-04 study. BMC Cancer 2016;16:153.
3. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer. N Engl J Med 2010;362:1273-81.
4. Valle JW, Wasan H, Lopes A, et al. Cediranib or placebo in combination with cisplatin and gemcitabine chemotherapy for patients with advanced biliary tract cancer (ABC-03): a randomised phase 2 trial. Lancet Oncol 2015;16:967-78.
5. Malka D, Cervera P, Foulon S, et al. Gemcitabine and oxaliplatin with or without cetuximab in advanced biliary-tract cancer (BINGO): a randomised, open-label, non-comparative phase 2 trial. Lancet Oncol 2014;15:819-28.
6. Phelip JM, Edeline J, Blanc JF, et al. Modified FOLFIRINOX versus CisGem first-line chemotherapy for locally advanced non resectable or metastatic biliary tract cancer (AMEBICA)-PRODIGE 38: Study protocol for a randomized controlled multicenter phase II/III study. Dig Liver Dis 2019;51:318-20.
8. Borad MJ, Champion MD, Egan JB, et al. Integrated Genomic Characterization Reveals Novel, Therapeutically Relevant Drug Targets in FGFR and EGFR Pathways in Sporadic Intrahepatic Cholangiocarcinoma. PLoS Genet 2014;10:e1004135.
9. Jusakul A, Cutcutache I, Yong CH, et al. Whole-Genome and Epigenomic Landscapes of Etiologically Distinct Subtypes of Cholangiocarcinoma. Cancer Discov 2017;7:1116-35.
10. Goyal L, Saha SK, Liu LY, et al. Polyclonal Secondary FGFR2 Mutations Drive Acquired Resistance to FGFR Inhibition in Patients with FGFR2 Fusion-Positive Cholangiocarcinoma. Cancer Discovery 2016.
11. Lowery MA, Abou-Alfa GK, Burris HA, et al. Phase I study of AG-120, an IDH1 mutant enzyme inhibitor: Results from the cholangiocarcinoma dose escalation and expansion cohorts. Journal of Clinical Oncology 2017;35:4015-.
12. Verlingue L, Malka D, Allorant A, et al. Precision medicine for patients with advanced biliary tract cancers: An effective strategy within the prospective MOSCATO-01 trial. European Journal of Cancer 2017;87:122-30.
13. Kwakman JJM, Simkens LHJ, van Rooijen JM, et al. Randomized phase III trial of S-1 versus capecitabine in the first-line treatment of metastatic colorectal cancer: SALTO study by the Dutch Colorectal Cancer Group. Annals of Oncology 2017;28:1288-93.
14. Hamaguchi T, Shimada Y, Mizusawa J, et al. Capecitabine versus S-1 as adjuvant chemotherapy for patients with stage III colorectal cancer (JCOG0910): an open-label, non-

inferiority, randomised, phase 3, multicentre trial. The lancet Gastroenterology & hepatology 2018;3:47-56.
15. Morizane C, Okusaka T, Mizusawa J et al. Combination gemcitabine plus S-1 versus gemcitabine plus cisplatin for advanced/recurrent biliary tract cancer: The FUGA-BT (JCOG1113) Randomized Phase III Clinical Trial. Ann Oncol 2019; 30: doi.org/10.1093/annonc/mdz402
1. Bridgewater J, Galle PR, Khan SA, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. J Hepatol 2014;60:1268-89.
2. Ebata T, Hirano S, Konishi M, et al. Randomized clinical trial of adjuvant gemcitabine chemotherapy versus observation in resected bile duct cancer. Br J Surg 2018;105:192-202.
3. Edeline J, Benabdelghani M, Bertaut A, et al. Gemcitabine and Oxaliplatin Chemotherapy or Surveillance in Resected Biliary Tract Cancer (PRODIGE 12-ACCORD 18-UNICANCER GI): A Randomized Phase III Study. Journal of Clinical Oncology 2019;0:JCO.18.00050.
4. Primrose JN, Fox R, Palmer DH, et al. Adjuvant capecitabine for biliary tract cancer: The BILCAP randomized study. Journal of Clinical Oncology 2017;35:4006-.
5. Lamarca A, Palmer DH, Wasan HS, et al. ABC-06 | A randomised phase III, multi-centre, open-label study of active symptom control (ASC) alone or ASC with oxaliplatin / 5-FU chemotherapy (ASC+mFOLFOX) for patients (pts) with locally advanced / metastatic biliary tract cancers (ABC) previously-treated with cisplatin/gemcitabine (CisGem) chemotherapy. Journal of Clinical Oncology 2019;37:4003-.
6. Golan T, Hammel P, Reni M, et al. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. New England Journal of Medicine 2019;0:null.
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