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. 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 (gemcitabine) and PRODIGE-12 (gemcitabine plus oxaliplatin) adjuvant studies were negative (arguably because they were small underpowered studies), BILCAP has established capecitabine as adjuvant therapy, with a median survival of over 50 months. The advanced biliary tract cancer (ABC) studies, primarily ABC-02, have established cisplatin and gemcitabine (CisGem) as standard first-line treatment. This is despite several challengers, including the FUGA-BT study comparing CisGem to gemcitabine plus S-1, presented in this issue of Annals. Second-line therapy has established FOLFOX as a standard of care, although the benefit was modest. 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. The active symptom control arm of the ABC-06 study 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, consistent driver alterations have been found in biliary tract cancer. 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. Importantly, these data will mandate tumour profiling for biliary tract cancers similar to that which has occurred for BRCA in adenocarcinoma of the pancreas, 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/m². There were also the added toxicities of fluoropyrimidine therapy (diarrhea, 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 S-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. 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. 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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