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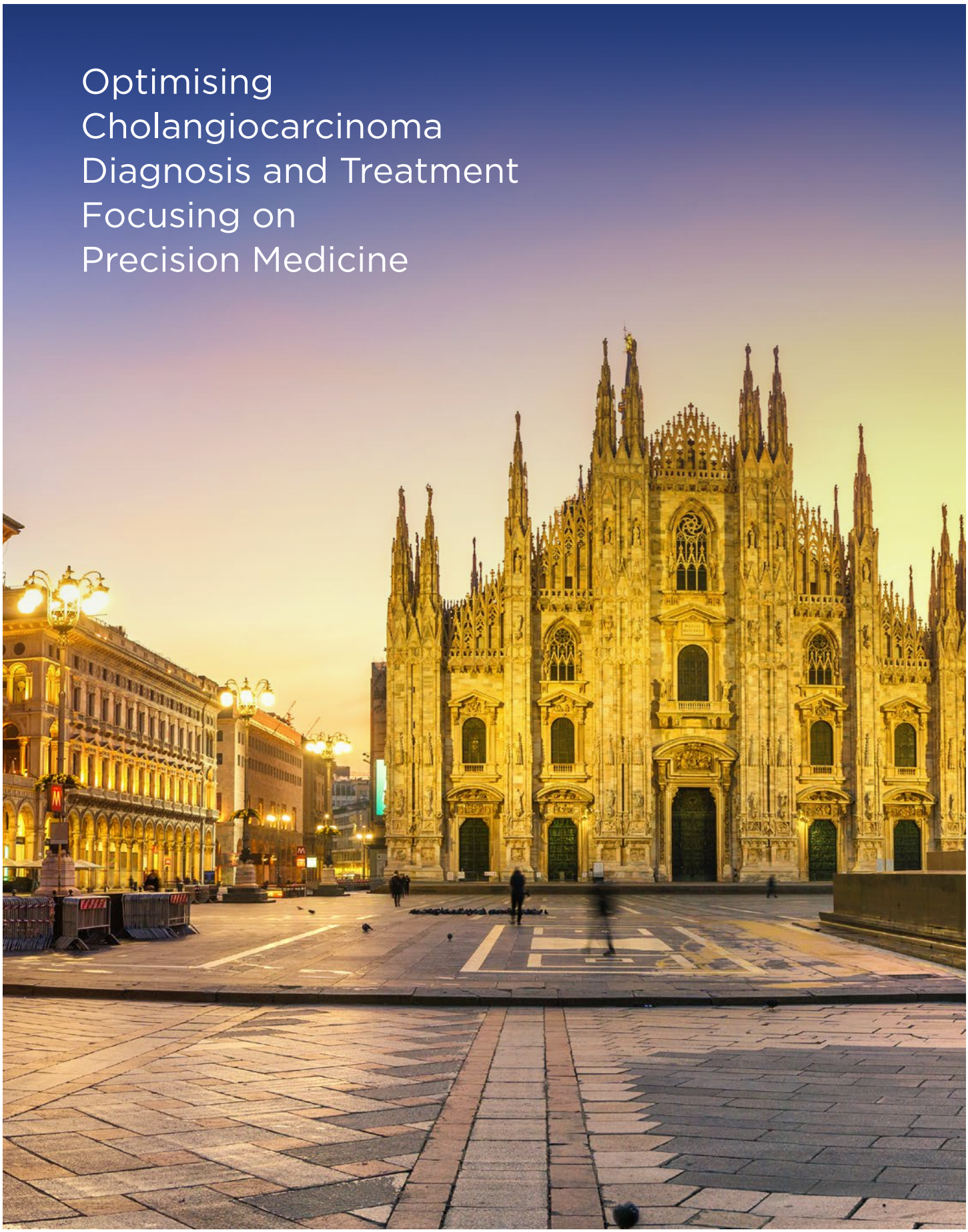

Optimising Cholangiocarcinoma Diagnosis and Treatment Focusing on Precision Medicine

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Abstract

This article is based on interviews conducted with Lorenza Rimassa, Arndt Vogel, and Harpreet Wasan. They provided their expert opinion on cholangiocarcinoma (CCA) diagnosis and treatment from their individual points of view. Through their extensive awareness and experience with this disease, they also provide practical clinical advice that can help reduce patient burden and improve outcomes. They uniformly agree that the key to better implement and advance precision medicine is streamlining the process of molecular testing. CCA treatment is expected to evolve rapidly once the results of several ongoing clinical trials are published. In the meantime, tumour boards help to decide what the best options are for each patient presented to them.

REDUCING PATIENT BURDEN BY IMPROVING AWARENESS

Lorenza Rimassa

Reducing patient burden is challenging in CCA (or biliary tract cancer) as patients and healthcare professionals (HCP) lack awareness about this disease. Patients are often diagnosed at advanced stages and the burden of the disease, the communication of the diagnosis, prognosis, and treatment are difficult. Extrahepatic CCA (eCCA) may manifest through jaundice, but intrahepatic CCA (iCCA) is usually asymptomatic, or it causes unspecific signs and symptoms (abdominal pain, nausea, weight loss).[1,2] Therefore, HCPs with little knowledge of CCA consider gastritis or other common diagnoses, rather than CCA, as a primary diagnosis. In most cases, patients undergo an ultrasound or upper endoscopy instead of CT scans. When patients and families are unaware of the existence of this disease, they do not ask for specific diagnostic tests or consider CCA as a possibility.

HCPs should provide the best information they can to each patient, particularly relating to specialised referral centres. These can better evaluate and treat patients with CCA, and offer new drugs through clinical trials or non-drug approaches (liver transplants, radiotherapy, radioembolisation).

Patient resources and associations are lacking, so they depend mostly on their relationship with their doctors. There is one large patient advocacy organisation in Europe, the Alan Morement Memorial Fund (AMMF).[3] This organisation increases awareness by organising professional meetings, using social media, and generally trying to reach physicians and laypeople to inform them about CCA and the importance of attending referral centres.[3] In addition, large oncology meetings should include sessions specific to liver cancer and CCA. Previously, these focused only on hepatocellular carcinoma, but now these liver cancer meetings also cover CCA.

Although the ideal priority is a timely diagnosis, it is often not the case. Timely referral of the patient to the best hospital or centre becomes critical for patients to receive appropriate treatment from the time they are diagnosed.

Healthcare Professionals Should Suspect Cholangiocarcinoma

Arndt Vogel

In the past, many patients were diagnosed with tumours of unknown origin but, in retrospect, those were clearly CCAs. Now, there are fewer tumours of unknown origin and more CCAs. In unclear cases, next-generation sequencing (NGS) can be valuable to better understand the type of tumour.

DIAGNOSTIC TESTING

Imaging

Lorenza Rimassa

The first test for suspected liver cancer or CCA should be CT scans of the abdomen and thorax as the most common sites of metastasis are the liver, abdominal and thoracic nodes, and lung and peritoneal metastases. For patients in earlier stages of the disease who are suitable for surgery or locoregional therapy, MRI can be helpful to define the extent of the disease.

Biopsies: Ensuring Availability of Tumour Tissue for Molecular and Genomic Testing

Lorenza Rimassa and Harpreet Wasan

Tissue core biopsies should, if possible, be obtained in CCA as a significant amount of tumour tissue is needed, whereas fine needle aspirations (FNA) only provide a few tumour cells. Two to three core biopsies are preferred to account for the stroma-rich structure of iCCA,[4] and to collect adequate tumour tissue, ensuring enough material for different tests. When patients undergo FNAs, they will likely need further biopsies, specifically for molecular characterisation. Patients usually accept these circumstances once they understand that it is important to clarify tumour characteristics, define prognosis, create a treatment plan, and check clinical trial eligibility. For iCCA, the most common method to collect core biopsies is ultrasound. For eCCA, it is even more crucial to

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stress the importance of collecting enough tissue as biopsies are often obtained via endoscopic approaches (FNAs or brush biopsies). FNAs are problematic due to the >70% rejection rates for RNA fusion testing in some clinical trials, whereas with core biopsies the failure rate is 5–15%, depending on the technology used. In CCA, a small subset of patients has surgery (20–30% of patients, depending on the country) with curative intent upfront. Assuming that the tumour profile upon relapse has not changed, and that the storage conditions did not alter the tumour tissue taken during the original sample, there may be sufficient tissue available for the different novel tests. Most patients face challenges with tissue testing because they present at an advanced or metastatic stage of their disease and are not surgical candidates, so samples are often limited.

Liquid Biopsies

Lorenza Rimassa

Liquid biopsies from blood drawn to find circulating tumour cells, DNA, or RNA are not yet used for diagnosis, but they are used in research.[5] They could be useful to follow up after targeted therapies to detect new treatment-resistant mutations that could be targeted by other drugs from the same class. In lung cancer, they are part of clinical practice to detect mutations responsible for resistance to targeted agents (epidermal growth factor receptor [EGFR] inhibitors).

DIAGNOSTIC TESTING WITH TUMOUR TISSUE BIOMARKERS

Lorenza Rimassa and Harpreet Wasan

Until recently, the histopathological diagnosis of advanced and metastatic CCA sufficed because only cytotoxic chemotherapy was an option. With the approval of pemigatinib (U.S. Food & Drug Administration [FDA], and the European Medicines Agency [EMA]),[6,7] and infigratinib and ivosidenib (FDA),[8] molecular information is now needed either through individual tests for *IDH* mutations through immunohistochemistry (IHC) and *FGFR* fusions through fluorescence *in situ* hybridisation (FISH), or preferably through wider panels with NGS, to obtain a complete molecular characterisation of the tumour. FISH and IHC are easier to obtain, but the problem is that they may use up tissue that is then insufficient for wider molecular testing; this is due to the often limited amount of tumour tissue available, even with core biopsies. On the contrary, NGS tests multiple alterations at the same time. However, in centres where only pemigatinib is available and there are no open trials, it is better to obtain FISH than nothing at all.

NGS cannot be performed in clinical practice in all centres or countries. For instance, in Italy NGS is not reimbursed by the national health system and is unavailable in clinical practice for patients with CCA. In such cases, enrolling recently diagnosed patients in clinical trials that offer candidates NGS during pre-screening can speed second-line therapeutic decisions when relapse inevitably occurs. If the patients are not eligible for the trial, the testing still helps to inform HCPs about the potential of other targetable or actionable alterations.

LOGISTICAL CHALLENGES

Arndt Vogel and Harpreet Wasan

Obtaining the Appropriate Molecular Testing to Detect *FGFR2* Fusions is Critical

First, in many CCAs, the adequacy of tissue biopsies is a major challenge; for iCCA it is potentially easier but for eCCA (for example, Klatskin tumours), access is more difficult. Patients diagnosed with FNA may start first-line cytotoxic treatment but, when they progress, a core biopsy will eventually be needed.

Second, iCCA is a stroma-rich tumour, so biopsies may have fewer and scattered tumour cells, which compromises RNA sequencing. HCPs need to know about the necessary testing and make sure core biopsies are obtained, and pathologists need to double-check whether biopsies are satisfactory; they should inform the clinician as soon as possible if the tumour cell content is low.

Third, the whole process to obtain molecular testing can take up to 2–3 months and, due to the frequently rapid progression of CCA, some

patients deteriorate rapidly while waiting for testing. This intricate process includes deciding when NGS is needed; obtaining adequate biopsies; checking if there are sufficient tumour cells for nucleic acid extraction (DNA and RNA); arranging logistics and reimbursement or insurance coverage for testing NGS, etc.; shipping time; sequencing; obtaining the result and interpreting, including less common molecular variants; deciding if patients have adequate performance status (fitness); and arranging reimbursement for fibroblast growth factor receptor (FGFR) inhibitors.

Having to specifically request RNA sequencing from the tumour sample is a recent requirement, and an efficient logistics pathway must be set up to sequence the tumour properly and expediently. Everyone involved, starting with the HCPs who take the biopsies, should be fully aware that several good core biopsies are needed. When *HER2* amplification testing for gastric cancer became the standard of care (SOC), specialists worked with gastroenterologists to ensure they took eight to ten biopsies from the primary tumour to have enough tumour cells for IHC (although the challenges of obtaining gastric biopsies are less than in CCA). The same conceptual approach should now be implemented for CCA as NGS and other tests become SOC options. Ideally, if oncologists immediately plan NGS once a CCA diagnosis is established, patients will benefit as this would avoid delays when they relapse on second-line and beyond. Delays would thus be avoided when tumour material is not available at relapse and the process needs to be re-initiated.

For patients with CCA, average survival is around 1 year,[9] so if molecular testing starts after the failure of first-line therapy, results may arrive too late for patient benefit. HCPs should, therefore, characterise the tumour early to know if there is a drug-targetable alteration and be prepared to plan second-line treatments in advance. In summary, the process to obtain this information needs to occur ideally before and during first-line treatment to have enough time to organise everything and start second-line treatment immediately on progression.

Additionally, patients may have partial molecular testing, but the platforms may either fail to test RNA fusions, or RNA platforms are not accessible: another reason why more tissue may be needed, which can be challenging in second-line and third-line patients. Lacking a unified method for diagnostic testing can also be problematic because it increases the need for a large amount of tumour tissue; one sample goes to diagnostic pathology, another to NGS with a platform for fusion testing, and others to test *HER2* and microsatellite instability (MSI) by IHC or FISH.

CHOLANGIOCARCINOMA TREATMENT

A Little History

Harpreet Wasan

In the early 2000s, a collaborative UK-wide group was formed to investigate whether a SOC could be established for advanced inoperable CCA. Two active drug candidates were identified, and ABC-01[10] was designed to investigate if a low-dose platinum drug added to gemcitabine would be safe and potentially improve survival for patients with CCA and gallbladder cancer. The ABC-01 trial was a pilot study that linked seamlessly to the ABC-02 randomised trial (n>400).[11] It resulted in significantly increased progression-free survival (PFS) and overall survival by almost 3 months.[11] This is how CisGem became the first-line SOC for CCA and gallbladder cancer, with Level 1 evidence for the first time. It is a very well-tolerated regimen and, until very recently (see section: 'Other New Developments'), no trial has been able to improve on the ABC-01 or -02 findings.

In the following years, a second-line treatment trial was developed. The recently published ABC-06 study[12] randomised patients to modified leucovorin, fluorouracil, and oxaliplatin (FOLFOX) versus active symptom control. Second-line patients' physical status and liver function deteriorate rapidly and it was not clear if their quality of life could be improved or if they benefitted in any way from chemotherapy. FOLFOX confirmed a small benefit in patients who previously progressed on CisGem.[12] Consequently, the ABC-06 regimen (fluoropyrimidine and oxaliplatin) is the cytotoxic chemotherapy established as second-line SOC, with Level 1 evidence.

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Meanwhile, two parallel developments have occurred: positive trials for patients with *FGFR* fusions; and *IDH* mutations supported the approval of pemigatinib[13] and ivosidenib[14] as second-line options. If patients have these specific aberrations genomically, they may benefit from these drugs. Since, all patients with CCA receive CisGem in first-line, but in second-line they can receive pemigatinib, ivosidenib, or FOLFOX, depending on whether they have any targetable mutations. Globally, irinotecan second-line (leucovorin, fluorouracil, irinotecan [FOLFIRI], or other irinotecan-based regimens) is also used, although this is not based on adequately powered randomised studies as with ABC-01, -02, and -06.[15-17]

Additionally, for patients with very rare CCA, with microsatellite unstable or high deficient MMR tumours, immunotherapy is an accepted SOC. Pembrolizumab[18] is licensed for MSI-high tumours irrespective of their site of origin and histology. Increasingly, *HER2* targeted therapies are used off-label in CCA, where *HER2* amplification is confirmed, and there are also many ongoing *HER2*-based CCA trials. Other drugs are used for alterations, such as *BRAF* mutations, and *NTRK* fusions.

The Current Standard of Care

Lorenzo Rimassa, Arndt Vogel, and Harpreet Wasan

In the advanced setting, the first-line treatment is CisGem. Patients have a median PFS of 6–8 months on first-line treatment, as in the ABC-01 and -02 study.[11] Depending on the individual cancer centre practice, treatment is administered until there is disease progression, or for 6 months (8 cycles) only initially. For patients who progress, modified FOLFOX may be used in second-line according to the ABC-06 trial, or targeted agents (pemigatinib, infigratinib, and ivosidenib) may be used, if applicable. As previously stated, the problem is having information about molecular alterations to determine if patients are eligible. If this information is unavailable, or they show there are no alterations, then they are treated with chemotherapy in second-line (FOLFOX or capecitabine plus oxaliplatin [CAPOX], or rarely FOLFIRI). Patients who receive targeted second-line therapies may receive FOLFOX in the third-line setting, or be enrolled in clinical trials.

As the UK established the ABC-01, -02, and -06 pathways, alternatives in patients not suitable or tolerant of infusion devices with a peripherally inserted central catheter or port can consider more convenient 3-weekly CAPOX, as there is significant user experience with this regimen in gastrointestinal cancer in general. This can avoid problems, especially infection risk with pump and infusion lines, and patients with CCA have a very high incidence of venous thromboembolism (22%).[19] FOLFOX and CAPOX are interchangeable in other cancers, so can be extrapolated for the convenience of the patients.[20] The number of visits with CAPOX is almost 50% lower than for FOLFOX, and fewer visits during the COVID-19 pandemic have become critical in healthcare delivery. If physicians are familiar with this regimen and know how to manage the toxicities, it is thus potentially better for both patients and institutions. Prescribing CAPOX is especially beneficial when working within socialised healthcare systems as it requires considerably fewer resources than FOLFOX and it costs less.

Incorporating Targeted Therapies into Clinical Practice

Lorenzo Rimassa and Arndt Vogel

Since pemigatinib was approved, it would not be appropriate for patients with *FGFR2* fusions to be treated with chemotherapy after a first-line treatment with CisGem. Patients with CCA should receive molecular testing as soon as possible to better assess what the best treatment for them would be in second-line.

HCPs should be fully aware of the clinical data regarding FGFR2 inhibitor efficacy and side effects. This therapy is just one option, and not all patients will respond. Overall, there is less toxicity, but when it is present, it can be severe. With FGFR inhibitors, side effects such as hyper- or hypophosphataemia, stomatitis, and nail and skin toxicities are common. Although these are oral drugs, follow-up should be frequent to talk with and examine patients, checking for skin toxicities and mucositis. Some patients are very keen to stay on the drug, and they do not mention side effects due to fear

of dose reductions or treatment interruptions. To avoid overuse and financial issues, timely imaging after 6–8 weeks is also important to identify non-responders.

NEW DEVELOPMENTS

Precision Medicine and New Options in the Pipeline

Lorenza Rimassa and Arndt Vogel

CCA research has rapidly evolved. With the introduction of NGS, it was obvious that CCA, despite being a rare tumour, had many interesting genetic alterations for which targeted therapies were available or could be developed (approximately 45% of patients with iCCA). These include *FGFR2* fusions, *IDH1* mutations, MSI-high, and less frequent mutations on *BRAF*, *HER2*, *BRCA*, and *NTRK*.

Precision medicine trials that enrol patients with CCA with specific genetic aberrations are important; there are many drugs available through these trials, unlike in clinical practice where only a few are available. For instance, for *FGFR2* fusions, three Phase III studies are currently underway in the first-line setting that seek to show the superiority of FGFR inhibitors (pemigatinib, infigratinib, and futibatinib) over CisGem.[21-23] These studies hold a lot of hope, because most patients with *FGFR2* fusions do not respond as well to chemotherapy as wild-type patients. Ivosidenib is being considered in first-line combined with CisGem.[24]

BRAF mutations in iCCA and *HER2* alterations (amplifications and mutations) in patients with eCCA are also being studied. The MyPathway study for eCCA has shown positive results with pertuzumab and trastuzumab in patients with *HER2* alterations requiring second-line treatment.[25] *BRAF* and mitogen-activated protein kinase kinase inhibitors (dabrafenib plus trametinib) were evaluated in the ROAR study in patients with *BRAF* mutated CCA, and showed a promising response and an acceptable safety profile.[26] Also, bispecific antibodies like zanidatamab[27] and small molecules such as neratinib[28] are being tested in patients with *HER2* alterations. *NTRK* and *RET* gene fusions and *BRCA* mutations may also be targetable. Although it varies from country to country, the availability of this variety of targeted treatments is why it is better to have all the molecular information through NGS.

Moreover, multidisciplinary molecular tumour boards are very important in precision medicine, because a group of experts that understand the genetic alterations and possible targeted therapies can make a better recommendation. In Germany, it is possible to apply for reimbursement outside of a clinical trial with a recommendation from a tumour board, based on convincing preclinical and Phase II clinical data. After the first reimbursement approval, other HCPs can prescribe a given therapy, provided that the individual patient's insurance will cover it. In countries where this is not possible, it is more complicated. HCPs could offer innovative targeted therapies within clinical trials; otherwise, the need to perform NGS can be questioned if there is no chance to use targeted therapies other than the few approved ones.

The Evolving Class Effect Concept for Fibroblast Growth Factor Receptor Inhibitors

Lorenzo Rimassa, Arndt Vogel, and Harpreet Wasan

There is a clear class effect for FGFR2 inhibitors, and many drugs are available, either approved or through trials. The first generation of FGFR2 inhibitors (pemigatinib, infigratinib, and derazantinib) has been followed by the next class (futibatinib and RLY-4008) that have activity against some resistant mutations and other genetic alterations and are more specific for *FGFR2*. Overall, all FGFR inhibitors work in patients with *FGFR2* fusions, but they are different types of molecules, which have different ways of reaching their targets, partial efficacy overlap, and slightly different safety profiles.

More information about a tumour's mechanisms of resistance will help in developing ways to sequence different drugs. In other words, it is not clear if a patient that becomes resistant to pemigatinib becomes resistant to the entire class, or only to pemigatinib. There are preliminary data from futibatinib in patients previously treated with other FGFR inhibitors.[29] Some

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patients responded to futibatinib even if they progressed on other FGFR inhibitors.[29] It should, therefore, be possible to use one FGFR inhibitor after another. In lung cancer, patients are treated with EGFR inhibitors, and when they become resistant, they are treated with newer generation EGFR inhibitors.

FGFR2 inhibitor sequencing also depends on how clinical trials are designed. Many of the trials for FGFR2 inhibitors exclude patients with previous FGFR2 exposure, so it is difficult to know if a different drug from the same class might have a better effect. Drug labelling for funding and reimbursement tend to match eligibility criteria from research trials and, because these are ongoing simultaneously, many of them will be based on pemigatinib-naïve patients, which complicates comparisons regarding efficacy after pemigatinib fails. This is a typical challenge in oncology. High-quality evidence may never be available, because it is simply too complex to run so many trials for subsets of patients with a rare cancer. Fortunately, real-world evidence will start emerging, although gathering the data may be challenging. Data can be collected from the UK's National Cancer Registration and Analysis Service (NCRAS) if the drugs are reimbursed. International data from countries with more flexibility on the coverage of follow-on drugs will be helpful as well.

Other New Developments

Lorenza Rimassa and Harpreet Wasan

There are already abundant data on immunotherapy in patients with MSI-high or mismatch repair deficiency. Combination therapies, including immunotherapies, could be promising in CCA. In October 2021, AstraZeneca published a press release about the TOPAZ study (CisGem plus durvalumab), saying it met the primary endpoint surpassing CisGem in the first-line setting,[30] and indicating the first-line SOC may change in the next few months.

There are also trials combining immunotherapy and chemotherapy with antiangiogenics. For bevacizumab, there is a randomised Phase II trial in first-line, testing CisGem, atezolizumab, and bevacizumab.[31] The rationale for combining chemotherapy, immunotherapy, and antiangiogenics exists because there may be a synergy between antiangiogenics and immune checkpoint inhibitors, since antiangiogenics may modulate the tumour microenvironment. Accordingly, they could increase the activity of immune checkpoint inhibitors, and perhaps be active in iCCA.

Antibody-drug conjugates are another alternative under investigation for colorectal cancer and CCA. These conjugates are already established in *HER2* positive breast cancer. The studies look promising because the cytotoxic component is more focused on the *HER2* cells with fewer systemic toxicities, and this concept could be applied to other proteins (isocitrate dehydrogenase and others).[32]

Regarding non-drug treatments, a few studies show that radioembolisation could constitute an additional option for iCCA,[33,34] and a clinical randomised trial in first-line ICCA (SIRCCA study) compared with CisGem alone is completed and awaiting final study results. Surgeons and interventional radiologists use other technologies, such as stereotactic body radiotherapy, in the current ABC-07 study for CCA.[35] Although these non-drug technologies are used to a degree, they should be integrated more as part of multimodal CCA treatment for the benefit of patients. In referral centres, every pathway should be discussed in tumour boards, including whether there are non-drug interventions that could help treat CCA.

SUMMARY

Lorenza Rimassa, Arndt Vogel, and Harpreet Wasan

The availability of FGFR2 inhibitors benefits patients. The speakers have had patients with *FGFR2* fusions who did not respond to chemotherapy but had good responses with pemigatinib (for up to 2 years). The most important point is to apply good molecular testing. *IDH1* mutations can be easily recognised using NGS, but it is more difficult for *FGFR2* fusions as they require RNA sequencing to be identified. Since many patients are tested with NGS, HCPs need to talk to pathologists about which tests are used and if they recognise *FGFR2* fusions. Importantly, everyone involved in the

diagnosis and treatment needs to be aware of the challenges in taking the biopsy to perform the test with RNA sequencing. Better awareness could help the majority of patients to receive these targeted therapies.

Achieving appropriate and timely molecular testing is key to achieving progress in CCA treatment, although this is often more challenging than the treatment. The experts agree that with better organisation, access to better care for patients would improve dramatically. Additionally, testing has prognostic value as it facilitates patient planning; patients with targetable alterations may survive longer than those without them (2–3 years versus 1 year). Ideally, tumour profiles would be obtained upon advanced cancer diagnosis or earlier and, consequently, drug sequencing could be planned and organised by the time patients require further lines of treatment.

FGFR2 fusions have positive predictive implications when FGFR inhibitor can be used, but the question is how these patients respond to chemotherapy and how these alterations relate to the natural history of CCA. There is consistent data for four inhibitors (pemigatinib, infigratinib, futibatinib, and derazantinib) regarding response, disease control rate, and PFS. More research is certainly needed to understand the natural history of these patients, and their different genetic alterations. All this information will allow HCPs to make even more progress to help patients with CCA.

Regulatory agencies and national health systems need time to adapt for precision medicine to be implemented in regular clinical practice. The approval of different targeted therapies for CCA (pemigatinib, ivosidenib, etc.) should encourage agencies to cover and reimburse NGS testing. Although it appears costly, using NGS widely to characterise the tumour and to make therapeutic decisions is the right way to obtain the needed information and make further progress on targeted therapies.

In the future, SOC will become more complex, with a continuum vertically and horizontally integrated across the complexities of a liver-oncology specific management team, to achieve the best outcomes for the patient. Drug and non-drug options should be considered upfront and every time the patient progresses. For targeted therapies in particular, a continuum of care closer to first-line choices will probably develop over the next few years. Studies will evaluate if it is better to administer isocitrate dehydrogenase 1 or FGFR2 inhibitors to patients first-line. Although they are established as second-line and third-line options, these targeted drugs with more tolerable safety profiles might be a better first-line option for subsets of patients who do not want cytotoxic chemotherapy, are intolerant to it, or have an advanced age.

The patients bear the burden of the diagnosis and the disease, but HCPs can help by providing appropriate information, especially about patient advocacy organisations, and the best testing and treatments available. It is important to increase awareness among primary care practitioners, and the public in general. This would empower HCPs to suspect CCA more frequently and order CT scans for screening, and for patients to ask for the appropriate testing to be done. In the next few years, practice-changing data will emerge and help to add more options to clinical practice.

References

1. Forner A et al. Clinical presentation, diagnosis and staging of cholangiocarcinoma. Liver Int. 2019;39(Suppl 1):98-107.
2. NORD. Rare disease database: cholangiocarcinoma. 2020. Available at: https://rarediseases.org/rare-diseases/cholangiocarcinoma/. Last accessed: 7 December 2021.
3. AMMF: The Cholangiocarcinoma Charity. AMMF homepage. Available at: https://ammf.org.uk/. Last accessed: 7 December 2021.
4. Banales JM et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. Nat Rev Gastroenterol Hepatol. 2020;17(9):557-88.
5. Lamarca A et al. Molecular targeted therapies: ready for "prime time" in biliary tract cancer. J Hepatol. 2020;73(1):170-85.
6. U.S. Food & Drug Administration (FDA). FDA grants accelerated approval to pemigatinib for cholangiocarcinoma with an FGFR2 rearrangement or fusion. 2020. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pemigatinib-cholangiocarcinoma-fgfr2-rearrangement-or-fusion. Last accessed: 7 December 2021.
7. European Medicines Agency (EMA).

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Pemazyre. 2018. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/pemazyre. Last accessed: 8 December 2021.

8. U.S. Food & Drug Administration (FDA). FDA grants accelerated approval to infigratinib for metastatic cholangiocarcinoma. 2021. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-infigratinib-metastatic-cholangiocarcinoma. Last accessed: 7 December 2021.
9. Rizzo A et al. Pemigatinib: hot topics behind the first approval of a targeted therapy in cholangiocarcinoma. Cancer Treat Res Commun. 2021;27:100337.
10. Valle JW et al. Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study - the UK ABC-01 study. Br J Cancer. 2009;101(4):621-7.
11. Valle J et al.; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362(14):1273-81.
12. Lamarca A et al.; Advanced Biliary Cancer Working Group. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol. 2021;22(5):690-701.
13. Abou-Alfa GK et al. Pemigatinib for previously treated locally advanced/metastatic cholangiocarcinoma (CCA): update of FIGHT-202. J Clin Oncol. 2021;39(Suppl 15):4086.
14. Zhu AX et al. Final overall survival efficacy results of ivosidenib for patients with advanced cholangiocarcinoma with IDH1 mutation: the phase 3 randomized clinical ClarIDHy trial. JAMA Oncol. 2021;7(11):1669–77.
15. Mizrahi JD et al. Multi-institutional retrospective analysis of FOLFIRI in patients with advanced biliary tract cancers. World J Gastrointest Oncol. 2020;12(1):83-91.
16. Endlicher E et al. Irinotecan plus gemcitabine and fluorouracil in advanced biliary tract cancer: a retrospective study. Digestion. 2016;93(3):229-33.
17. Yoo C et al. Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (NIFTY): a multicentre, open-label, randomised, phase 2b study. Lancet Oncol. 2021;22(11):1560-72.
18. Keytruda. Is Keytruda right for you? 2021. Available at: https://www.keytruda.com/msi-h/treatment-options/. Last accessed: 7 December 2021.
19. Khanuja J et al. Biliary tract cancers and the associated risk of venous thromboembolism. J Clin Oncol. 2019;37(Suppl 4):304.
20. Marabella C. 3-month adjuvant CAPOX represents potential option for select high-risk stage II CRC. 2021. Available at: https://www.onclive.com/view/3-month-adjuvant-capox-represents-potential-option-for-select-high-risk-stage-ii-crc. Last accessed: 7 December 2021.
21. Incyte Corporation. A study to evaluate the efficacy and safety of pemigatinib versus chemotherapy in unresectable or metastatic cholangiocarcinoma (FIGHT-302). NCT03656536. https://clinicaltrials.gov/ct2/show/NCT03656536.
22. QED Therapeutics, Inc. Phase 3 study of BGJ398 (oral infigratinib) in first line cholangiocarcinoma with FGFR2 gene fusions/translocations. NCT03773302. https://clinicaltrials.gov/ct2/show/NCT03773302.
23. Taiho Oncology, Inc. Futibatinib versus gemcitabine-cisplatin chemotherapy as first-line treatment of patients with advanced cholangiocarcinoma harboring FGFR2 gene rearrangements (FOENIX-CCA3). NCT04093362. https://clinicaltrials.gov/ct2/show/NCT04093362.
24. Academic and Community Cancer Research United. Gemcitabine and cisplatin with ivosidenib or pemigatinib for the treatment of unresectable or metastatic cholangiocarcinoma. NCT04088188. https://clinicaltrials.gov/ct2/show/NCT04088188.
25. Javle M et al. Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): a multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol. 2021;22(9):1290-300.
26. Subbiah V et al. Dabrafenib plus trametinib in patients with BRAF V600E-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial. Lancet Oncol. 2020;21(9):1234-43.
27. Meric-Bernstam F et al. Zanidatamab (ZW25) in HER2-positive biliary tract cancers (BTCs): results from a phase I study. J Clin Oncol. 2021;39(Suppl 3):299.
28. Business Wire. Puma Biotechnology presents interim results from the biliary tract cancers cohort of the phase II SUMMIT "Basket" trial of neratinib at ASCO GI. 2021. Available at: https://www.businesswire.com/news/home/20210115005058/en/Puma-Biotechnology-Presents-Interim-Results-from-the-Biliary-Tract-Cancers-Cohort-of-the-Phase-II-SUMMIT-%E2%80%9CBasket%E2%80%9D-Trial-of-Neratinib-at-ASCO-GI. Last accessed: 7 December 2021.
29. Goyal L et al. TAS-120 overcomes resistance to ATP-competitive FGFR inhibitors in patients with FGFR2 fusion-positive intrahepatic cholangiocarcinoma. Cancer Discov. 2019;9(8):1064-79.
30. AstraZeneca. Imfinzi plus chemotherapy significantly improved overall survival in 1st-line advanced biliary tract cancer in TOPAZ-1 phase III trial at interim analysis. 2021. Available at: https://www.astrazeneca.com/media-centre/press-releases/2021/imfinzi-improved-survival-in-biliary-tract-cancer.html. Last accessed: 7 December 2021.
31. Hack SP et al. IMbrave 151: a randomized phase II trial of atezolizumab combined with bevacizumab and chemotherapy in patients with advanced biliary tract cancer. Ther Adv Med Oncol. 2021;13:17588359211036544.
32. Criscitiello C et al. Antibody-drug conjugates in solid tumors: a look into novel targets. J Hematol Oncol. 2021;14(1):20.
33. Edeline J et al. Radioembolization plus chemotherapy for first-line treatment of locally advanced intrahepatic cholangiocarcinoma: a phase 2 clinical trial. JAMA Oncol. 2020;6(1):51-9.
34. Helmberger T et al. Real-world outcomes of patients with intrahepatic cholangiocarcinoma treated with trans-arterial radioembolization: results from the CIRSE registry for SIR-spheres therapy (CIRT), a large European prospective multi-center observational study. J Clin Oncol. 2021;39(3):308.
35. Cancer Research UK. A trial looking at stereotactic body radiotherapy and chemotherapy for people with locally advanced bile duct cancer (ABC-07). 2021. Available at: https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-chemotherapy-stereotactic-radiotherapy-people-locally-advanced-bile-duct-cancer-abc-07. Last accessed: 7 December 2021.