Advances in cholangiocarcinoma research: Report from the third Cholangiocarcinoma Foundation Annual Conference

William Chapman
Washington University School of Medicine in St. Louis

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Introduction

Despite a few global regions with increased incidence, cancers of the biliary tract remain a rare entity. Cholangiocarcinoma has been referred to as an ‘orphan’ cancer, given its relative infrequency in the Western population. Most patients are diagnosed at an advanced disease stage which contributes to a 5-year survival that is less than 10% (1). Although cholangiocarcinoma remains relatively rare, the incidence of intrahepatic cholangiocarcinoma has been rising worldwide over the past decade (2) and thanks to the relentless advocacy efforts of the Cholangiocarcinoma Foundation and focused research from a few investigators, advances in the molecular description of the entity have recently been seen (3). The potential for targeted therapies to address several mutational changes, added to the new discoveries in immunotherapy has led experts to rethink the entity of biliary cancers and to view the disease through a new lens as summarized herein.

This communique summarizes the thoughts of some of the world’s experts in biliary cancer as they challenged each other in debates and lecture discussions on multi-varied subjects as part of the Third Annual Cholangiocarcinoma Foundation Meeting that was held in Salt Lake City, Utah between February 3 and 5, 2016.

Surgical resection and liver transplantation

Surgical resection of cholangiocarcinoma remains the only potentially curable therapy and is rarely feasible except in intrahepatic cholangiocarcinoma where tumors are commonly located at or near the junction of the left and right hepatic ducts. This location at the biliary confluence near the bifurcation of the portal vein and the right hepatic artery accounts for the challenges of adequate surgical resection. Even in the absence of distant spread, achieving negative bile duct margins, leaving behind adequate liver remnant function, and maintaining adequate portal and arterial inflow to the liver remnant is a difficult task. When resection is being considered, the goal is to completely remove all tumor tissue (R0 resection) maintaining an adequate liver remnant. An incomplete (R2: grossly involved margin) resection is probably futile and any potential benefit too small to justify the surgical risk. The biliary extent of
the tumor should allow a margin negative resection and permit technically feasible reconstruction of the biliary tree, with an adequate remnant liver volume, usually at least 30% of the total liver volume. Studies examining the outcomes of patients with cholangiocarcinoma who undergo surgery with curative intent find a median overall survival of 34 months. Several prognostic factors may identify subgroups of patients with better survival. In patients with R0 resection, median overall survival rates of 60 to 65 months are reported. In addition, a negative lymph node status, well-differentiated tumor grade, and papillary phenotype are independent predictors of favorable survival. Unfortunately, the high rate of recurrence in the remnant liver is associated with a 5-year survival of only 20–30% in most series of patients undergoing partial hepatic resection. This has led to investigation of liver transplantation as a strategy for curative therapy for this dismal disease. Current reports using neoadjuvant chemoradiation in conjunction with liver transplantation demonstrate 5-year survival rates of 50–70% in highly selected patients with hilar cholangiocarcinoma (4). Current criteria include use of this approach in patients with unresectable tumors less than 3 cm in greatest dimension, in the absence of intrahepatic or regional nodal involvement, and in whom transperitoneal biopsies have not been performed. While promising, this approach can only be utilized in highly selected patients. Improved diagnostic studies and earlier detection are greatly needed to allow more patients to be eligible for curative therapy. Intrahepatic cholangiocarcinoma is generally considered a contraindication for liver transplantation at most centers, however results for patients with solitary tumors less than 3 cm in size, in the setting of underlying cirrhosis, suggest that this therapy has similar success rates to transplantation in patients undergoing transplant for hilar tumors. While efforts continue to help better define the role of transplantation, future studies should also focus on refining surgical techniques, expanding minimally invasive approaches, and finding better adjuvant treatments to reduce the high recurrence rate.

**Adjuvant therapy for cholangiocarcinoma: different views**

The role of adjuvant therapy following curative resection of cholangiocarcinoma is uncertain. While some cancer characteristics have been identified which clearly increase the risk for tumor recurrence (1)—multifocality, lymph node and margin-positive disease—the rarity and heterogeneity of the disease has made the conduct of classic randomized studies very difficult. Therefore, adjuvant therapy guidelines reflect consensus statements and literature reviews; for example, patients in whom adjuvant therapy did not provide a significant improvement in survival (5). Within this report, a subset analysis suggested that patients who were left with positive lymph nodes or R1 resection margins derived the most benefit for adjuvant chemoradiation or chemotherapy. But the applicability of this observation has the limitation of any retrospective data set, reflecting the lack of consistency in the extent and details of surgery. A very small number of intrahepatic cholangiocarcinoma cases were included in this meta-analysis and therefore the benefit of adjuvant therapy in intrahepatic cholangiocarcinoma is unproven. In cases of extrahepatic (hilar) cholangiocarcinoma, the Mayo clinic experience has highlighted the role of liver transplantation in those with unresectable disease (4). While there are a range of opinions, until there are better data available, the presented meta-analysis by Horgan et al. makes reasonable and rationale recommendations for managing patients.

Similarly, the role for radiation for cholangiocarcinoma has come under scrutiny; recommendations largely stem from observations that radiotherapy does not affect survival in pancreatic cancer, which is the data source behind much of the rationale. However, larger scale genomic studies confirm that cholangiocarcinoma has much lower rates of mutant KRAS, which preclinical studies have shown confers radio-resistance (6–8). This observation is backed by clinical observations that mutant KRAS tumors have worse outcomes than wild type KRAS in rectal cancer, lung stereotactic body radiation therapy (SBRT), and liver SBRT. Additionally, local control, particularly in extrahepatic cholangiocarcinoma, appears to be a dominant failure pattern, and associated with quality of life issues. More data that supports the role of radiation include the recently published phase II study of protons in inoperable intrahepatic cholangiocarcinoma demonstrating 2-yr local control of 95% (9). Additionally, a study by Southwest Oncology Co-operative Group (SWOG) evaluating gemcitabine plus capecitabine followed by chemoradiation demonstrated a much lower local failure than historical surgical series (10). Further formal evaluations of the role of radiation in cholangiocarcinoma are needed.

In summary, adjuvant treatment with systemic chemotherapy or chemoradiation is still not standard of care for most patients with cholangiocarcinoma. Patients with multifocal, node or margin positive disease should be considered for clinical trials of adjuvant therapy. Ongoing
international trials will offer insight in this regard. The recent SWOG phase II trial enrolled patients with extrahepatic cholangiocarcinoma or gallbladder cancer who were treated with systemic chemotherapy (gemcitabine plus capecitabine) followed by chemoradiation (5). A total of 79 eligible patients were treated; the 2-year survival was 65%, whereas it was 67% and 60% in R0 and R1 patients, respectively. Median overall survival was 35 months. This regimen is therefore considered as effective as an adjuvant approach. The same group has planned a randomized controlled trial for extrahepatic cholangiocarcinoma. Targeted therapeutics represents a promising strategy for advanced cholangiocarcinoma. Recent genomic sequencing studies have identified a host of genetic aberrations that are potentially targetable. These include ERBB2, IDH1, FGFR and B-RAF mutations (6,11,12).

Systemic therapy: one-size fits all or custom-made therapy?

In the setting of advanced (locally advanced, recurrent or metastatic) biliary tract cancers, systemic chemotherapy with gemcitabine plus cisplatin has become the reference regimen, based on the results of the ABC-02 study (13). In this study, patients who met standard eligibility criteria (e.g., performance status 0–1, baseline bilirubin level ≤1.5× upper limit of normal and adequate renal function) were included as long as the cancer was biliary in origin. While it is widely acknowledged that within the term “cholangiocarcinoma” there are different subgroups of patients based on anatomy—extrahepatic, extrahepatic and gallbladder—as well as on different molecular signatures (14), an assessment of the magnitude of benefit of gemcitabine plus cisplatin was constant in ABC-02 across the different diagnoses, an effect maintained when Japanese patients were also evaluated (15). This confuses the question of whether to look at the entire population or at subsets when exploring new treatment options.

The establishment of standard chemotherapy regimens for cholangiocarcinoma is a recent phenomenon (the first effective cholangiocarcinoma regimen was identified in 2010 vs. the first regimens for colorectal cancer established in the 1950s). Fluoropyrimidines (5-FU and capecitabine) along with gemcitabine and platinum compounds appear to be active. However, to date, no biomarkers have been identified to predict who will respond to chemotherapy, and the pressures to find active therapies are balanced against the challenges of improving outcomes in patients who often have disease courses complicated by compromised liver function and infections, for example.

On the other hand, there are “actionable” targets in the biliary tract. The first generation of studies has targeted the epithelial growth factor receptor. Despite the encouraging results of the early phase II, single arm study of cetuximab in addition to the gemcitabine/oxaliplatin combination (GemOx) (16), four randomized studies [adding cetuximab (two studies) (17,18) erlotinib (19) or panitumumab (20) respectively to the GemOx regimen] have now failed to demonstrate a PFS or OS improvement over chemotherapy alone, highlighting the need for randomized trials to truly evaluate the potential benefit of novel agents. Retrospectively, it will be important to identify, if possible, if there were any subgroups of patients who did derive benefit within the whole study population of those studies.

At present, chemotherapy as a “one-size-fits all” remains one of the cornerstone of treatment (along with surgery and radiotherapy); much as it remains in other cancers such as breast cancer, colorectal cancer and lung cancer where targeted therapies are also being increasingly used. However, advances in DNA sequencing technologies have enabled the identification of common tumor mutations in biliary tract cancers, including IDH1, IDH2, FGFR2, mismatch repair proteins, and ERBB2 (21,22). The frequency of certain mutations is associated with tumor location, with significantly different incidences for intrahepatic, extrahepatic, and gall bladder sites of cancer. The genetic heterogeneity between individual biliary tract cancers suggests that treatment should be individualized, or “custom-made”, according to tumor mutation status in some cases. In support of this hypothesis, clinical trials of several novel targeted agents for genetically-defined subsets of biliary tract cancers show promising efficacy, including the IDH1 inhibitor, AG-120, for IDH1-1-mutant cholangiocarcinoma (23), the pan-FGFR inhibitor BGJ398 for intrahepatic cholangiocarcinoma harboring FGFR2 gene fusions or other FGFR pathway aberrations (24), and the immune checkpoint inhibitor pembrolizumab for biliary tract cancers with defects in mismatch repair genes (25). These exciting data support ongoing efforts to better define anatomic, molecular, and genetic subsets of biliary tract cancers for stratification and enrichment in clinical trials of targeted therapies to identify patients most likely to respond, so that we may move towards custom-made therapy for patients suffering from this complex and heterogeneous family of cancers.
Molecular profiling of biliary cancers: the future of therapy

Whole exome and transcriptome sequencing of biliary tract cancers has provided key insights into the heterogeneity of molecular alterations among cancers arising at different sites along the biliary tract and a strong rationale for the development of molecularly targeted therapies. While FGFR2 gene fusions and IDH1/2 and BAP1 mutations are found in intrahepatic cholangiocarcinoma, PRKACA/PRKACB fusions, ELF3 and ARID1B mutations occur preferentially in extrahepatic cholangiocarcinoma while aberrations in ERBB2/3, EGFR, PTEN and mutations in TERT promoter gene have been described in gallbladder cancers (26). A poor prognosis subtype characterized by high mutational load and increased immune checkpoint activity has been identified across all sites, and may predict for response to immune checkpoint inhibitors. Optimally, patients will be selected for targeted therapy based on molecular profiling. Ongoing clinical trials are evaluating the use of TRK, ALK and ROS-1 inhibitors in patients with NTRK or ROS-1 rearrangements, and FGFR inhibitors in patients with FGFR2 fusions, while inhibitors of IDH1/2 and ERBB2/3 are also in clinical development in genetically selected populations. The wealth of therapeutic targets identified by molecular profiling offers promise for integration of targeted therapy with chemotherapy, and hopes for a significant improvement in patient outcomes over the coming decade.

Based on the previous section, one may wonder if molecular profiling is justified for all patients with cholangiocarcinoma at this point in time. The end goal of tumor profiling is the application of personalized medicine to optimize therapeutic benefit and minimize toxicity or unnecessary exposure to side effects. The application of molecular profiling for the treatment of biliary cancers faces challenges related to the heterogeneity of the disease, the prioritization of targets as well as identification of driver alterations, the clonal evolution of cancer and several other microenvironment and stromal pressures which impact the biology of this cancer in a global manner. It has become clear that relevant therapeutic targets can be elucidated through molecular profiling such fusions in FGFR or mutations in IDH1 and amplifications in Her2. These continue to be relatively rare and vary based on the site of origin of the biliary cancer (intra-versus extrahepatic). To optimize the application of molecular profiling, it would be prudent to follow careful algorithms to prioritize molecular alterations, to account for tumor heterogeneity and clonal evolution (possibly through liquid biopsies), and to account for the effect of the epigenome and the microenvironment on the tumor. Lastly, emerging research suggests that integrative molecular analysis approaches can help to classify biliary cancers into specific subgroups with distinct molecular signatures that are associated with prognosis and that may in turn offer opportunities for tailored treatment approaches aimed at more global signatures. In summary, there is jewel in the haystack as some molecular alterations may offer excellent therapeutic opportunities but advancing the treatment of this complex disease also requires a more global understanding of the biology and likely combinations of therapies.

A special type of intrahepatic cholangiocarcinoma: fluke-worm related cholangiocarcinoma

Liver flukes are the foodborne parasites dwelling in the biliary tract. Based on epidemiologic data and animal models, the infection of two liver flukes, *Opisthorchis viverrini* and *Clonorchis sinensis*, is strongly associated with intrahepatic cholangiocarcinoma in humans. People get infected with liver flukes by eating raw freshwater fish, and it has been hypothesized that chronic fluke infection and both endo- and exogenous nitrosamine formation causes intrahepatic cholangiocarcinoma in Northeastern Thailand, with the world’s highest incidence of the disease. Although, the “top-down” mass anti-helminthic therapy could lower the infection prevalence in the past two decades, re-infection is still the major challenge for intrahepatic cholangiocarcinoma prevention. Therefore, researchers at Khon-Kaen University have initiated a “bottom up” strategy to establish a durable healthy ecosystem led by the community. Following the successful pilot project, it has been expanded to other areas in Northeastern Thailand (27).

Although the clinical presentations of fluke-associated intrahepatic cholangiocarcinoma are similar to non-fluke associated ones, fluke-associated intrahepatic cholangiocarcinoma tend to occur at the hilar or perihilar bile ducts. Molecular differences between fluke- and non-fluke associated with intrahepatic cholangiocarcinoma have been identified in mRNA expression, gene mutation and microRNA expression profiles. Currently, there is no difference in management of fluke- and non-fluke associated intrahepatic cholangiocarcinoma. However, based on molecular differences, we can look forward to different treatment for these two entities.
The potential for immunotherapy in biliary tract cancer

Immune checkpoint inhibition leads to durable tumor control and shrinkage in a subset of patients with a variety of advanced malignancies. Immune checkpoint blockade has translated into a significant overall survival advantage in comparison to established therapies in some metastatic solid tumors (28). A critical question is whether immune checkpoint blockade will lead to clinical benefit and improved survival in patients with cholangiocarcinoma. Emerging preclinical data suggest that a subset of biliary tract cancers are recognized by the immune system but undergo a complex process of immune editing, which allows biliary tract cancers to evade an anticancer immune response. Furthermore, stromal factors, such as carcinoma associated fibroblasts, may exclude and exhaust effector T lymphocytes, leading to biliary tract cancers’ immune privilege. Preliminary clinical data indicate that some patients with biliary tract cancers respond to immune checkpoint blockade and several studies are now planned or ongoing to define the role of this novel therapeutic approach.

CCA genetics and cancer detection

The major identified risk factors for CCA are underlying inflammatory disorders, and transcriptional profiling of intrahepatic CCA has revealed a subset of cancers with an inflammatory STAT3 signature. In addition, genome sequencing studies suggest that chromatin modifiers are frequently disrupted in this disease suggesting intrahepatic CCA may be a disease of epigenetic chromatin modification. Gain-of-function mutations in the isocitrateg dehydrogenase (IDH) gene are one potential mechanism for epigenetic dysregulation, as the mutant enzyme catalyzes the formation of the oncometabolite 2-hydroxyglutaric acid, which inhibits histone demethylases. Mutations in IDH are rare in most epithelial tumors but relatively common in CCA, and trials with IDH inhibitors for patients with activating mutations are underway. Fibroblast growth factor receptor 2 (FGFR2) fusions are also common in intrahepatic CCA, and recent studies suggest that the pan-FGFR inhibitor BGJ398 may be active in treating cancers with these gene fusion aberrations (29). In contrast to intrahepatic CCA, PRKACA and PRKACB fusion genes are common in perihilar CCA and presumably are targetable. CCA is also a highly desmoplastic cancer with a rich stroma characterized by cancer associated fibroblasts (CAF). Preclinical data suggest that CAF are susceptible to a class of drugs termed BH3 mimetics and that targeting CAF with these agents may have an anti-tumor effect in CCA (30).

The analysis of 38 CCA samples from The Cancer Genome Atlas project (TCGA), including mutations, methylation, copy number, RNA, miRNA, and protein platforms was reported (Lawrence N. Kwong, new unpublished data). A meta-analysis of all published sequencing data to date in >500 fluke-negative intrahepatic cholangiocarcinoma samples revealed potential mutual exclusivity of PIK3CA and TP53 mutations as well as KRAS and IDH mutations. Should these exclusivities hold up in larger cohorts, they could form a partial basis for classifying cholangiocarcinoma with therapeutic implications given the rapid development of PI3K pathway, MAPK pathway, and IDH inhibitors? The TCGA analysis identified a distinct cross-platform signature of IDH mutant samples which included specific copy number profiles, methylation profiles, and most critically, expression profiles that were enriched for increased oxidative phosphorylation and decreased chromatin modifier signatures. Moreover, several IDH-wild type samples were found to resemble IDH mutant samples in both expression and copy number profile. Overall, these studies provide an initial step towards identifying clinically-relevant molecular classifications of intrahepatic cholangiocarcinoma with therapeutic implications given recent and ongoing efforts to develop inhibitors of oxidative phosphorylation epigenetic modifiers.

Using the paradigm of pancreatic cancer, another highly lethal malignancy for which most patients are unresectable at the time of diagnosis, early detection of cholangiocarcinoma could employ the same leukopheresis to enrich the number of cells recovered. Rhim described efforts to detect tumor-associated DNA sequences in patient-derived material, including circulating tumor cells (CTCs), exosomes, and as cell free DNA in the plasma. Digital droplet PCR, which allows for highly sensitive amplification of DNA when a template is present, has been adapted for this so that approximately 250 different amplicons of interest can be amplified for sequencing.

Metabolism and epigenetics

With respect to mutant IDH, metabolism is important. By focusing on metabolic pathways that are limiting for the proliferation of cancer cells in different environmental and tissue contexts, Vander Heiden found that nucleotide synthesis is often limiting, and that the tumor cell of origin...
Animal models

The liver is well known for its regenerative capacity, which under normal circumstances is mediated by the replication of existing cells. What has become clear over the last few years is that many forms of liver injury are also accompanied by substantial cellular plasticity, whereby hepatocytes become converted into cells with many or most cholangiocyte features. This phenomenon of cellular plasticity was touched upon in several talks from the last session, which dealt with the role of plasticity in normal liver regeneration, showing that hepatocytes may co-opt the process during progression.

Data also suggest that intrahepatic cholangiocarcinoma can also arise from cholangiocytes (33). Forbes used a strain of mice in which Cre recombinase could be activated in cholangiocytes in a tamoxifen-inducible manner (CK19-Cre). Using this strain, in combination with a lineage marker, his group deleted p53 specifically in the biliary compartment. When these manipulations were combined with administration of the carcinogen thioacetamide (TAA), they developed intrahepatic cholangiocarcinomas over a 6-month period, demonstrated a clear biliary origin of the tumors. Based on these studies, it appears that intrahepatic cholangiocarcinoma can arise from either cholangiocytes or hepatocytes in the right context. Forbes also showed data regarding the role of Wnt and Notch signaling in CCA pathogenesis. Analysis of human tissue revealed that the stromal macrophages surrounding intrahepatic cholangiocarcinomas express Wnt ligands. Moreover, the Wnt pathway activity progressively increases during pre-malignant progression, suggesting that Wnt pathway inhibitors (e.g., inhibitors of the Wnt regulator porcupine) could have therapeutic benefit in CCA.

Obviously there are pros and cons to the various model systems. In particular, one may ask if the genetically engineered mouse model of CCA which incorporates mutations in IDH and Kras (34) and then went on to describe a high-throughput screen in which a panel of CCA cell lines was pitted against a library of clinically-relevant compounds. Comparing the responses of the CCA cell lines to those of >600 cell lines derived from other solid tumor types revealed that CCA lines bearing IDH mutations had a distinct response profile. In particular, mutant CCA cells exhibited extreme sensitivity to a class of kinase inhibitors. By applying CRISPR/Cas9-based genome editing, the key mediators of drug sensitivity were defined, enabling the creation of a new clinical trial for intrahepatic cholangiocarcinoma patients with IDH mutations.

CCF grant recipient talks

In 2015, the CCF awarded its first research fellowships—one-year grants to junior investigators to pursue CCA research and the first afternoon session featured four short talks by the first cohort of Fellowship recipients. Allyson Merrell began by speaking about the cellular origins of CCA, an area of some controversy in the field. Because
CCA exhibits histological features of ducts, tumors were thought to arise from duct-lining cholangiocytes (or biliary epithelial cells). However, different laboratories have shown, using lineage tracing in the mouse, that both hepatocytes and biliary epithelial cells can give rise to CCA depending on the oncogenes used and other experimental details. Merrell is systematically testing different mutations in both cell types to clarify the connection between cell of origin, mutational spectrum, and resulting tumor type. As cellular plasticity is an important feature of normal liver injury, these findings may reflect a connection between the multiple cells of origin and the frequent mutation of epigenetic regulators in CCA.

Next, Katsuyuki Miyabe spoke about his studies regarding fibroblast growth factor receptor (FGFR) gene family aberrations in CCA, hypothesizing that FGFR receptor aberrations other than the known mutations in FGFR2 might play a pathogenic role. RNA sequencing of 9 cases of CCA samples showed that several FGF ligands and FGFR4 are expressed at significantly lower levels when compared to 119 normal liver samples from the GTex database. Moreover, RNA sequencing has also detected new fusions of potential interest. Miyabe found that multiple FGFR inhibitors (ponatinib, dovitinib, BGJ398) inhibited the growth of LIV31 CCA xenografts (with FGFR fusions), with BGJ398 being the most potent. This xenograft model could be used in the future to select the FGFR inhibitor which works best for a given patient’s fusion.

Daniela Sia provided further insight into the role of FGFR2 fusions in CCA. As prior work showed a novel FGFR2-PPHLN1 fusion event in 16% of intrahepatic cholangiocarcinoma patients, Sia tested the impact of this aberration by injecting mice with FGFR2-PPHLN1—expressing cells, showing enhanced tumor growth rates compared to mice injected with empty vector. The most dramatic effects were seen during the initial phase of tumor growth. Treatment of FGFR2-PPHLN1—expressing HUCCT1 xenografts with a FGFR2 inhibitor, BGJ398, induced decreased tumor growth compared to the placebo group with no apparent signs of toxicity. Similar efficacy of BGJ398 was observed in vitro in cell lines expressing other FGFR fusion proteins, including FGFR2-BICC1.

Chad Walesky described how he is using the zebrafish to study the influence of developmental pathways on CCA pathogenesis. Specifically, he is focusing on potential interactions between the Wnt/β-catenin pathway and hepatocyte nuclear factor 4 alpha (HNF4α), molecules that are involved in the development of the liver as well as CCA. Studies in the laboratory have shown that knockdown of HNF4α in the zebrafish leads to a reduction in hepatocyte differentiation while genetic or chemical increase in β-catenin results in a loss of HNF4α and a maintenance of cholangiocyte differentiation. Based on these findings, it is hypothesized that activation of β-catenin results in a loss of HNF4, causing hepatoblasts to preferentially differentiate into cholangiocytes.

Conclusions

The work described herein gives an in-depth summary of the current approaches to treatment and translation for cholangiocarcinoma. This conference also brought together a broad collection of clinical and scientific investigators sharing the common goal of understanding and combatting cholangiocarcinoma. As exemplified by several of the talks, this type of fundamental understanding has already led to the development of patient-specific therapeutic approaches that can be tested in clinical trials. Other approaches, including immunotherapy, are viewed with great excitement, but will require more of the same type of basic understanding for progress to be made. More importantly, it helps identify the unanswered questions and challenges which require cross-disciplinary collaboration and strong advocacy to resolve and overcome.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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