Drug Development Platform for Cholangiocarcinoma

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Contributor: Brinda Balasubramanian

Cholangiocarcinoma (CCA), a group of malignancies that originate from the biliary tract, is associated with a high mortality rate and a concerning increase in worldwide incidence. In Thailand, where the incidence of CCA is the highest, the socioeconomic burden is severe. Yet, treatment options are limited, with surgical resection being the only form of treatment with curative intent. The current standard-of-care remains to be adjuvant and palliative chemotherapy which is ineffective in most patients. The overall survival rate is dismal, even after surgical resection and the tumor heterogeneity further complicates treatment. Together, this makes CCA a significant burden in Southeast Asia. For effective management of CCA, treatment must be tailored to each patient, individually, for which an assortment of targeted therapies must be available

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1. Introduction

Cholangiocarcinoma (CCA) is a group of malignancies which originate from the biliary tract with increasing worldwide incidence in the last decade [1]. The socioeconomic burden of CCA is severe, particularly in the Southeast Asia. Thailand has the highest CCA incidence, where it is almost 100 times more prevalent (85 per 100,000) than Western countries (0.8–2 in 100,000) [2]. The alarming mortality rate of 14%, which roughly translates to 20,000 deaths every year, makes CCA a cause for concern [3]. Treatment is challenging as it is usually asymptomatic in the early stages and diagnosed in the advanced stages, with dismal prognosis and a discouraging 7–20% 5-year survival rate [4][5]. Surgical resection and liver transplant, the only form of treatment with curative intent, are technically challenging and require specially trained personnel [6]. The median survival time following surgical resection is 15 months; the 3-year survival rate of 35 to 50% is achieved almost exclusively in patients with a negative histological margin at the time of surgery [7][8][9]. Nevertheless, even after surgical resection, the cancer recurrence rate is high [10]. Adjuvant chemotherapy after surgical resection has been expected to overcome recurrence, yet they do not lengthen the overall survival [11]. Moreover, surgical resection is limited to patients diagnosed in the early stages. CCA patients in advanced stages, that present with local invasion or distant metastasis, are generally inoperable, restricting their treatment options to solely palliative chemotherapy [12]. The overall survival for patients with unresectable tumor is just under 12 months from diagnosis.

CCA is highly heterogenous in terms of tumor pathology, genetics, primary origin, risk factors, epidemiology, and clinical features [13][14], all of which further complicate treatment. Generally, CCA is classified into intrahepatic (iCCA) and extrahepatic (perihilar or distal) subtypes based on the anatomical location of primary [15][16]. In clinical

trials, the different CCA subtypes are generally pooled together, because, the heterogeneity within the subtypes is unclear until recent advances in molecular characterization techniques such as next-generation sequencing (NGS) [17]. Genetic profiling studies using NGS have elucidated the distinct molecular profiles present in intrahepatic and extrahepatic CCA [18]. Altogether, the inadequate patient stratification in clinical trials often results in poor outcomes and trial failure. Currently, physicians are compelled to treat CCA patients with the premise “one size fits all” due to the lack of available therapeutic alternatives. Precision medicine in cancer, also known as “precision oncology”, considers the heterogeneity of cancer and thus abandoning the “one size fits all” premise. It combines different aspects of molecular profiling to appropriately inform diagnosis, prognosis, and thereby customizing treatment for patients, individually [19]. This is practiced in high-income countries (HICs) for prevalent cancers such those of the lung, breast, etc., to predict treatment outcomes in patients [20]. However, this is yet to be practiced in CCA patients, particularly, in low and middle-income countries (LMICs) in Southeast Asia. Increasing evidence supports the use of guided targeted therapies to improve overall survival for CCA patients [21][22][23][24][25]. Therefore, considering the heterogeneity of CCA, treatment should be tailored to individual patients with targeted therapy.

Molecular and mutational profiling studies using NGS have elucidated a number of biomarkers exclusive for CCA [26] and since then, several targeted therapy drugs have emerged in CCA in recent years to meet the urgent demand for novel therapeutic options. Despite the increasing number of clinical trials in CCA, there is still a lack of targeted therapy drugs available for treatment. A majority of clinical trials with targeted therapy drugs fail to meet their endpoint objectives, mainly because a mixed cohort of patients are recruited to the study, as a consequence, the test drugs result in poor outcomes and fail to get regulatory approval [27]. This highlights the urgency of developing targeted therapy drugs for CCA and the need for an effective clinical trial platform to expedite the process.

In this review, we propose that the implementation of co-clinical trials will expedite the approval of targeted therapy drugs in CCA by improving trial outcomes. The primary objective of co-clinical trials is to conduct pre-clinical and clinical studies in parallel to allow for real-time integration of data for an effective study design in clinical trial, consequently improving the outcomes for clinical trials. Improved outcomes from clinical trials will encourage the approval of targeted therapy drugs for the selected cohort of CCA patients.

2. Current Standard-of-Care in CCA Management

Treatment options for CCA patients are stratified based on disease progression. For patients in early stages, surgery with curative intent followed by adjuvant chemotherapy with capecitabine is the current standard-of-care [28]. Whereas, patients in advanced stages are limited to palliative chemotherapy, a combination of gemcitabine and cisplatin, as first-line standard-of-care [29][30]. However, many patients are not well enough to receive aggressive systemic therapy. While some patients may benefit from the current standard-of-care, others fail to respond to first-line chemotherapy, possibly, due to the aggressive and heterogeneous nature of CCA [31]. For such patients, there has been no second-line standard-of-care until the ABC-06 phase III clinical trial in patients with locally advanced and metastatic biliary tract cancers [NCT01926236]. In this randomized clinical trial, the patients were given FOLFOX (a combination of folinic acid, 5-FU, and oxaliplatin) or ASC (i.e., proactive

management of biliary obstruction/sepsis, etc.). The median overall survival of the study arm that was treated with FOLFOX was 6.2 months as opposed to the 5.3 months of the standard arm. As this outcome was clinically significant, FOLFOX is now considered as the second-line chemotherapy for patients that were previously treated with gemcitabine and cisplatin. Nevertheless, the difference in the median overall survival between the two study groups is still modest. In addition, the long-term effects in a larger patient sample group are yet to be evaluated. There is increasing evidence that supports the use of guided targeted therapy drugs to overcome resistance to chemotherapy, by accurately treating patients according to their distinct molecular profiles [31]. That said, there is still a lack of approved targeted therapies available for CCA treatment. Therefore, effective treatment will only be possible once there is an abundance of targeted therapy drugs available to practice precision medicine in CCA.

3. The Current Landscape of Targeted Therapies in CCA

The onset of molecular profiling of tumors using NGS technology has contributed to a better understanding of the distinct genetic profiles in CCA. Several studies have identified potential targetable mutations and pathways for treatment. Moreover, these studies have elucidated the molecular discrepancies between the subtypes of CCA. Mutations in the genes *isocitrate dehydrogenases* (*IDH1* and *2*) and fusions of the *fibroblast growth factor receptor* 2 (*FGFR2*) were found exclusively in iCCA, whereas *Kirsten rat sarcoma viral oncogene homolog* (*KRAS*) were more common in eCCA [32]. Acknowledging this, and combined with the increasing evidence that advocates the use of targeted therapies, the research attention in CCA has driven towards the development of targeted therapy. However, despite the increase in clinical trials investigating targeted therapies, there is still a lack of it to practice precision medicine in CCA. We posit that this is due to the failure of clinical trials in yielding substantial outcomes. The prime reasons for clinical trial failure in CCA are due to inadequate stratifications of patients and a lack of understanding of the underlying mechanisms of drug response and acquired resistance elicited by certain compounds.

Targeted therapy drugs are anticipated to be incorporated into the treatment regimen based on clinical trial outcomes. Currently, inhibitors of *IDH* and *FGFR* are being investigated in clinical trials following encouraging preliminary results for specific cohorts of patients containing *IDH* mutations [NCT02989857] and *FGFR2* fusions [NCT03656536, NCT03773302]. Hence, biomarker driven clinical trials are expected to facilitate drug development, because, in such trials, the patients are stratified according to the oncogenic driver genes expressed and are more likely to respond to targeted therapy [33]. Yet, many other clinical trials involving potential targeted therapy drugs have failed in CCA. Several such clinical trials fail to recruit the patients conforming to the study designs, for example, studies investigating the effect of ceritinib in *ROS, ALK* mutations positive CCA patients were prematurely terminated due to insufficient recruitment of patients [NCT02374489, NCT02638909]. Several other targeted therapy clinical trials have failed to achieve their endpoint objectives due to study design constraints. Vandetanib, a multiple kinases inhibitor, was tried in patients with advanced metastatic CCA and did not improve progression free survival [NCT00753675] [34]. As the trial was randomized and patients were not stratified based on molecular profiling of the tumors, the failure to achieve endpoint objectives could possibly be due to the tumor heterogeneity amongst the patients. Varlitinib, a pan-HER inhibitor, also failed to meet primary endpoint objectives in CCA

patients that failed first-line treatment [NCT02609958]. A clinical trial of bortezomib, proteasome inhibitor, was prematurely discontinued because of the lack of partial response [NCT00085410]. It is challenging to incorporate the tumor heterogeneity of the recruited patients in the study design. Additionally, without fully understanding the underlying mechanisms of the disease, there can be inconsistencies in tumor response when translated from in vitro to in vivo, and to the clinical setting. Therefore, inadequate stratification of patients can lead to inconclusive outcomes of the clinical trials.

Evidently, infigratinib (BGJ398), a selective FGFR inhibitor, has exhibited promising outcomes in a CCA patient cohort containing the *FGFR2* fusions. However, almost all patients eventually develop resistance due to acquired secondary mutations [35]. The evaluation of such clinical studies is based on tumor response and not directed towards understanding the underlying molecular mechanism of action of the drugs, this leads to the possibility of acquired resistance mechanism without any means to overcome the issue. Nevertheless, the urgency for accurate treatment for CCA patients is compelling and the need for targeted therapy, to treat different subsets of patients with distinct molecular signature, is imminent. Therefore, it is noteworthy that the FDA granted accelerated approval for pemigatinib, a novel FGFR inhibitor, to be used in treatment of CCA patients that are positive for *FGFR2* fusions and have failed first line chemotherapy [36] based on outcomes from a multi-cohort Phase II clinical trial [NCT04096417]. Currently, pemigatinib is in Phase III clinical trials as first-line treatment for CCA patients with *FGFR2* fusions. The accelerated approval by the FDA has expedited the drug development of pemigatinib and urged it towards clinical use. This is proof-of-concept that biomarker driven stratification of the patients results in a better outcome of clinical trials. Altogether, this suggests that the current clinical trial platform is lethargic in meeting the urgent need for novel therapeutics for CCA treatment, yet, when patients are accurately stratified and treated accordingly, there are improved outcomes in clinical trials.

Failed trials in HICs are not encouraged for further investigation in the LMICs, despite possible discrepancies in patient response to the drugs. Moreover, the clinical trials for CCA are designed and conducted based on the research of CCA patients in HICs. Due to this fact, many patients, particularly those in LMICs, are impeded from possibly effective therapies. Moreover, the rising costs of research and development discourage the LMICs to drive novel drugs for development, despite the growing demand. Hence, for effective management of CCA, research attention should be focused on driving more targeted therapy drugs towards approval. Consequently, this highlights that a more proficient system of clinical trials, which not only expedites the drug development process but also considers tumor heterogeneity and underlying mechanism of drug response, is needed to increase the chances of regulatory approval of targeted therapy drugs for CCA treatment.

4. What Are Co-Clinical Trials?

The co-clinical project was first established as a platform for translational research in cancer to cure acute promyelocytic leukemia (APL) [37]. This platform utilizes the advancement of preclinical models, that can accurately replicate tumor heterogeneity, to stratify patients into treatable subtypes. The main objective of this platform is to fast track the development of drugs to practice precision oncology, so that treatment can be tailored to patients, individually [38]. The co-clinical trial platform is expected to reduce the disparity that exists between pre-clinical

studies and clinical trials by conducting both the studies in parallel, in contrast to the sequential order in the conventional drug development process.

Currently, the drug development process for targeted therapies in CCA follows the conventional model which is both time-consuming and labor intensive. It roughly takes about 10–20 years for a candidate drug in its journey from the bench to the bedside [38] and only 13% of all drugs in clinical trials are FDA approved [39]. The schematics of co-clinical trials compared to conventional clinical trials is represented in Figure 1.

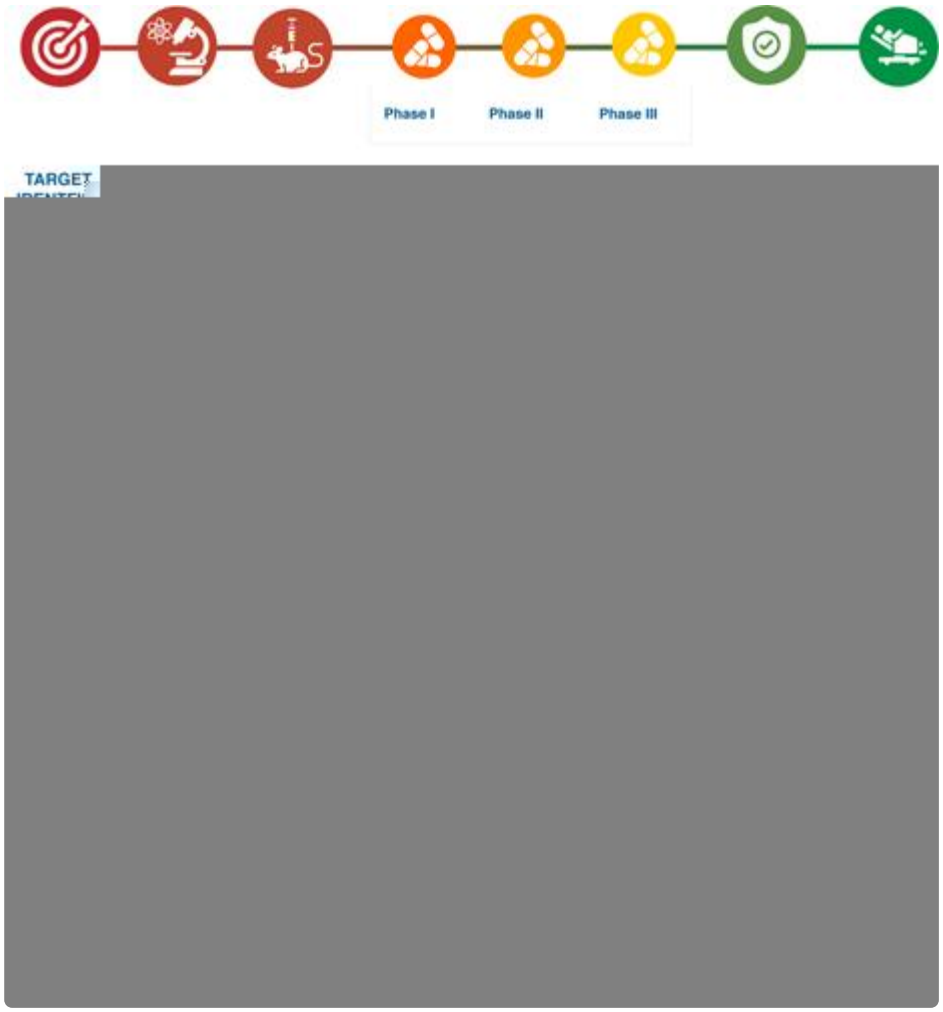

Figure 1. The conventional drug development process versus co-clinical trials**.** The different phases of clinical trials in the conventional drug development process take approximately 10–20 years for regulatory approval of the candidate drugs. Preclinical studies with animal models and clinical trials are conducted concurrently in co-clinical trials. The real-time data integration between the two parallel studies can accurately stratify patients into resistant or sensitive subtypes. The patients classified into resistant subtypes can be tested for enrolment in other existing clinical trials. The patient cohorts of the sensitive phenotype are then recruited to the trial with the animal study conducted in parallel. This will improve trial outcomes for candidate drugs and therefore encourage regulatory approval.

The concept of co-clinical trial is to simultaneously conduct both human clinical trials and preclinical testing (also known as “mouse hospital”). Initially, patients that meet the criteria of the clinical study will be recruited, much like the initial stages of a conventional clinical trial. Subsequently, molecular profiling of the tumor tissues from the patients will identify the appropriate animal models to be used in the study, which will be conducted in parallel to the human clinical trials. For pre-clinical testing, the animal models are set up with a similar treatment, disease-monitoring and result acquisition protocols. The data from the pre-clinical studies are shared in real-time to inform drug response and resistance in patients in the clinical study. Patients can be stratified into subtypes based on the drug response from the representative animal models [40]. Hence, pre-clinical studies can inform outcomes of the clinical study so that it can be optimized, thereby improving outcomes of the clinical trials and enabling the discovery of potential therapies for cancer treatment.

5. Co-Clinical Trials to Accelerate Drug Development in CCA

Co-clinical trials are expected to improve drug development of targeted therapies in CCA by improving clinical trial outcomes. The initial drug screening in the pre-clinical studies, using animal models, allows for rapid stratifications of the patient population based on drug response and resistance. Patient population can be stratified into resistant or sensitive subtypes based on the outcomes from the pre-clinical studies. Patients with resistant subtypes can be removed from the study as they are unlikely to respond to that particular treatment, hence, this is expected to improve clinical trial outcomes for candidate drugs by limiting the patient cohort to the sensitive subtype. For the most part, candidate drugs fail to reproduce the tumor response in a clinical setting when translating from pre-clinical studies because they are performed separately. In co-clinical trials, the candidate drugs are tested in preclinical animal models, that represent the genetic subtypes of patients, using the same protocol that is to be used in the clinical trials. The results between both the studies are shared in real-time so that the treatment protocol can be adjusted and optimized to achieve the best possible outcomes [40]. This reduces the gap between preclinical research, clinical testing, and patient care by facilitating collaborative studies between academic and clinical researchers, thereby curbing the time taken for clinical trials. The rapid stratification of patients into potential responders and non-responders based on experimental validation is expected to improve clinical trial outcomes and therefore expedite drug development in cancer. Therefore, co-clinical trials are expected to considerably improve the clinical trial outcomes in CCA and consequently, accelerate the drug development process and encourage more drugs to be available for treatment.

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