Optimization of systemic treatments for patients with biliary tract cancer

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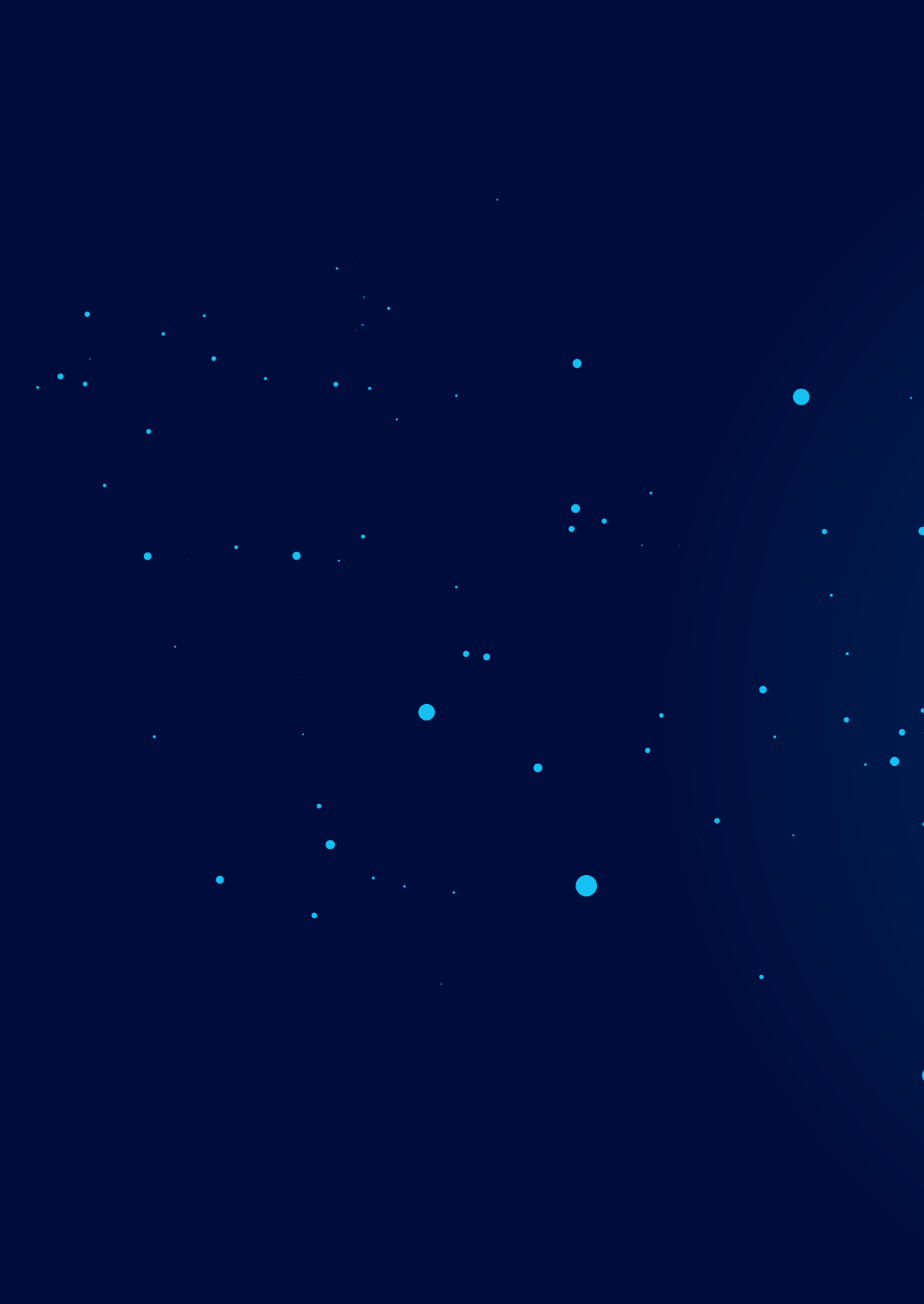

1 CHAPTER

General introduction and thesis outline

GENERAL INTRODUCTION AND THESIS OUTLINE

Biliary tract cancer is a group of malignancies arising from the epithelium of the bile ducts (i.e. cholangiocarcinoma) and the gallbladder. Cholangiocarcinoma is anatomically divided in three subtypes: intrahepatic, perihilar, and distal cholangiocarcinoma. The intrahepatic cholangiocarcinoma is originated from the bile ducts within the liver. The perihilar cholangiocarcinoma, also known as Klatskin tumour, arises in the liver hilium including the confluence of the right and left hepatic bile ducts. The third subtype is formed by distal cholangiocarcinoma which arises from the distal common bile duct. The three subtypes of cholangiocarcinoma and the gallbladder carcinoma form a heterogeneous group with different risk factors, diagnostic work-up and treatment options.[1]

The incidence of biliary tract cancer differs geographically between Western and East-Asian countries. In Europe and North America is the incidence of biliary tract cancer low (approximately 1-2 per 100.000 persons per year) compared to Asian country, especially North Thailand, China and Japan.[2,3] In the Netherlands approximately 1,000 patients are diagnosed over the last years with biliary tract cancer annually.[4] The incidence of cholangiocarcinoma is increasing because of rising incidence of intrahepatic cholangiocarcinoma as seen in other European countries and North America.[2,5-7] The perihilar cholangiocarcinoma accounts for approximately 50-60% of cholangiocarcinoma's while distal and intrahepatic cholangiocarcinoma for approximately 20-30% and 10-20%, respectively.[8] The intrahepatic cholangiocarcinoma is the most common primary liver tumour after hepatocellular carcinoma.[9]

The geographical variation in the incidence of biliary tract cancer is caused by the difference in risk factors between those regions.[7] The risk factors for cholangiocarcinoma include primary sclerosing cholangitis, hepatitis B and C infection, nonalcoholic fatty liver disease, high alcohol consumption and tobacco smoking.[10] In East-Asian countries biliary tract infection with liver flukes (Opisthorchis viverrini) are more common.[11] Cholecystolithiasis is the most common risk factor for gallbladder cancer.[12]

Patients with biliary tract cancer present often with an advanced stage disease; approximately 80% of them have locally advanced or metastastic disease at presentation.[7,13,14] Most patients with biliary tract cancer are asymptomatic or have nonspecific symptoms.[7] Patients with intrahepatic cholangiocarcinoma may present with abdominal pain in the right upper quadrant of the abdomen while patients with perihilar and distal cholangiocarcinoma may present with icterus due to biliary tract obstruction and sometimes fever due to cholangitis.[7,15] Gallbladder carcinoma is often incidentally found during cholecystectomie for cholecystolithiasis or on imaging for other reasons.[7,16]

In this thesis, the treatment approach for patients with biliary tract cancer in daily practice is explored. The main aim of this thesis was to evaluate the effectiveness of available systemic treatments in daily practice using population-based data, and to

identify subgroups of patients that may benefit most from these treatments. Additionally, we aimed to study the feasibility and efficacy of FOLFIRINOX as a second- line treatment for biliary tract cancer. The thesis is subdivided in three parts. In Part I outcomes of adjuvant treatment for resected biliary tract cancer are discussed. In Part II potential treatments for initially unresectable and non-metastatic biliary tract cancer and their outcomes are evaluated. In Part III we discuss the outcomes of first-line and second-line treatments for unresectable and/or metastatic biliary tract cancer and their prognostic factors.

Part I Adjuvant treatment for resected biliary tract cancer

A minority of patients (approximately 20%-30%) present with a potentially resectable disease at diagnosis and receive surgical resection with curative intent.[17,18] The five-year overall survival after surgical resection for biliary tract cancer remains poor (10%-40%) because of the high recurrence-rate.[17-21] Approximately two of three patients develop disease recurrence within five years after surgical resection.[17-21] The local recurrence pattern is predominantly seen in patients with cholangiocarcinoma whereas distant metastases are mainly seen in patients with gallbladder carcinoma.[17,19]

Adjuvant chemotherapy has been studied in patients with biliary tract cancer to increase loco-regional control, prevent distant metastasis and improve survival.[22] The American Society of Clinical Oncology (ASCO) clinical practice recommends capecitabine as a standard adjuvant treatment for biliary tract cancer based on the results of the BILCAP trial.[13,23] However, this clinical trial showed only significantly longer overall survival in per-protocol analysis but not in the intention-to-treat analysis.[23] The European Association for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) guidelines recommend adjuvant capecitabine.[24,25] In the Netherlands, adjuvant capecitabine is not adapted as the standard treatment by the Dutch Society of Medical Oncology (NVMO) because of limited clinical benefit. The BCAT and PRODIGE-12 clinical trials did not show survival benefit from adjuvant gemcitabine monotherapy and gemcitabine plus oxaliplatin compared to only surgical resection, respectively.[21,26] The role of adjuvant chemotherapy after resection is still a matter of debate.[22] The definitive results of the ASCOT trial (S1 versus observation) are awaited.[27] The ACTICCA-01 trial is ongoing and will find out whether gemcitabine plus cisplatin is more effective than capecitabine.[28] Based on the results of current clinical trials, it seems that only selected

patients may benefit from adjuvant therapy. We reviewed the available literature and assessed the outcomes of adjuvant therapy in daily clinical practice to identify subgroups of patients that may benefit from adjuvant therapy.

Part II Treatments for initially unresectable and non-metastatic biliary tract cancer

The optimal treatment approach for patients with initially unresectable and non-metastatic biliary tract cancer is unclear. Approximately half of the patients with advanced disease have initially unresectable and non-metastatic disease.[13,14] These

patients may have extra regional lymph node metastases or involvement of the major blood vessels that radical resection is not possible. These patients are treated currently with gemcitabine plus cisplatin as provide in the metastatic setting.[29]

Induction therapy

The ESMO guidline (2016) guideline recommends clinicians to re-discuss patients with initially unresectable and non-metastatic disease with good response to systemic or locoregional treatment in multi-disciplinary teams for surgical resection. Induction chemotherapy in selected patients may lead to downstaging and possible surgical resection with curative intent as shown by two meta-analyses for initially unresectable and non-metastatic gallbladder cancer.[30] The value of induction therapy in initially unresectable and non-metastatic cholangiocarcinoma was unclear. We performed a systematic review and meta-analysis to assess the value of induction therapy in initially unresectable and non-metastatic intrahepatic and perihilar cholangiocarcinoma.

Palliative systemic treatments and chemoradiotherapy

The NCCN guideline suggest various treatment options, including gemcitabine-based, fluoropyrimidine-based chemotherapy, chemoradiotherapy, or radiotherapy based on results from phase 2 trials or retrospective studies. The ESMO guideline suggest chemoradiotherapy in selected patients with biliary tract cancer. The role of chemoradiotherapy in patients with initially unresectable and non-metastatic disease is unclear. Studies on the efficacy of current standard treatment and various systemic treatments in initially unresectable and non-metastatic biliary tract cancer were scare. evaluated the use and outcomes of chemoradiotherapy and various systemic therapies in daily clinical practice as used in patients with initially unresectable and non-metastatic biliary tract cancer.

Part III Treatments for unresectable and/or metastatic biliary tract cancer

First-line treatment

Systemic chemotherapy has shown longer overall survival and improved quality of life compared to best supportive care in patients with unresectable and/or metastatic biliary tract cancer.[31] Currently, gemcitabine plus cisplatin is the standard first-line treatment for advanced biliary tract cancer based on the results of the ABC-02 trial.[29] This clinical trial has shown longer median overall survival (11.7 versus 8.1 months) and progression-free survival (8.0 versus 5.0 months) in patients treated with gemcitabine plus cisplatin compared to gemcitabine alone.[29] These findings were also confirmed by the Japanese BT22-trial which showed an overall survival (11.2 versus 7.7 months) and progression- free survival (5.8 versus 3.7 months) in the gemcitabine plus cisplatin arm versus gemcitabine arm.[32] Before this publication, gemcitabine monotherapy was regularly given as first-line treatment for patients with biliary tract cancer.[33] The ESMO guideline recommends using gemcitabine plus oxaliplatin as the first-line treatment for patients with biliary tract cancer and kidney injury.[34] However, the effectiveness of gemcitabine plus oxaliplatin has not been directly compared to that of gemcitabine plus cisplatin in patients with cholangiocarcinoma, except in one clinical trial for gallbladder cancer.[35] Recently, the FUGA-BT Phase III clinical trial demonstrated that first-line treatment with gemcitabine plus S-1 is not inferior to gemcitabine plus cisplatin.[36] Another phase III clinical trial suggested longer overall survival (median 13·5 months versus 12·6 months) in patients treated with the triplet gemcitabine, cisplatin plus S-1 compared to gemcitabine plus cisplatin.[37] However, the Kaplan-Meier survival curves for overall survival crossed each other twice, suggesting that there was no significant OS benefit from gemcitabine, cisplatin plus S-1 compared to gemcitabine plus cisplatin.

The combination of immune checkpoint inhibitors, durvalumab (TOPAZ–1 trial; HR 0.80, 95% CI 0.66–0.97) or pembrolizumab (KEYNOTE–966 trial; HR 0.83, 95% CI 0.72–0.95), in combination with gemcitabine plus cisplatin, resulted in significantly longer overall survival compared to gemcitabine plus cisplatin.[38,39] As a result, these two combinations are currently considered as alternative first-line treatments.[38,39] The role of targeted therapy is under investigation. Most clinical trials included patients age < 65 years with good performance status. The use and outcomes of systemic treatments in daily clinical practice, especially in patients aged >65 years, is not well studied. We evaluated the use and outcomes of systemic treatments for unresectable and/or metastatic biliary tract cancer in the population-based SEER-medicare and the Netherlands Cancer Registry.

Second-line treatment

Before the publication of the ABC-06 phase III trial in 2021, there was no standard second-line treatment after disease progression or unacceptable adverse events of first line chemotherapy.[40] We conducted a phase II study to evaluate the efficacy and safety of the combination fluorouracil, leucovorin, irinotecan plus oxaliplatin (FOLFIRINOX) in 30 patients with unresectable and/or metastatic biliary tract cancer previously treated with gemcitabine plus cisplatin. The primary endpoints were safety and efficacy (defined as objective response rate).

In 2021, the results of the ABC-06 phase III clinical trial were presented. The second-line treatment with folinic acid, fluorouracil, and oxaliplatin (modified FOLFOX) showed limited survival benefit compared to active symptom control (median overall survival of 6.2 months versus 5.3 months, respectively).[41] Modified FOLFOX is adapted as the standard second-line treatment.

Biomarkers for systemic therapy efficacy

Biomarkers that predict therapy efficacy are important in rare diseases with poor prognosis such as biliary tract cancer. It is known that selection of a treatment based on individual profiles results in better outcomes. In absence of standard biomarkers for systemic therapy efficacy, we conducted a systematic review to identify potential biomarkers for chemotherapy efficacy.

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