

# Impressive Result of Gemcitabine and Cisplatin Combination Therapy in Post-Operative Residual Cholangiocarcinoma Patient Presenting with Hyperbilirubinemia, an Experience in Indonesian Tertiary Hospital

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## Abstract

**Introduction:** Cholangiocarcinoma (CCA) often presents at an inoperable or an advanced stage in which complete resection is not possible. In such scenario, chemotherapy often is the only option to improve patient's survival. Severe hyperbilirubinemia, often associated with higher risk of developing chemotherapy-related adverse event, might complicates one's decision in choosing chemotherapy regimen. **Case Report:** We present a case of 63-year-old post-operative CCA patient with residual mass and severe hyperbilirubinemia. The patient completed six cycles of gemcitabine (1000 mg/m<sup>2</sup>, day 1 and 8) and cisplatin (70 mg/m<sup>2</sup>, day 1) every 3 weeks with tolerable side effect. No sign of residual tumor was observed on CT-Scan performed one-month post chemotherapy. **Conclusion:** Combination of cisplatin and gemcitabine may offer safe treatment option for post-operative residual CCA patient presenting with hyperbilirubinemia.

**Keywords:** *Cholangiocarcinoma; Gemcitabine; Cisplatin; Chemotherapy; Hyperbilirubinemia; Indonesia*

## Introduction

Cholangiocarcinoma (CCA) is one of the least commonly found type of cancer with worldwide incidence of less than 2/100,000 per year and 5-year survival rate of <10%. In the last two decades, the incidence and mortality rate of CCA have been increasing steadily.<sup>1,2</sup> Little is known about CCA in Indonesia. Epidemiological data of CCA in Indonesia

currently doesn't exist and detailed case report of CCA from Indonesia is very rare.

## Case Report

A 63-year-old female presented with progressive jaundice for two months, along with pruritus, dark yellow colored urine, frequent diarrhea (approximately six times per

day), and epigastric pain over the same time period. She didn't have significant past medical history. Family history included a daughter who passed away at the age of 42 years old due to breast cancer.

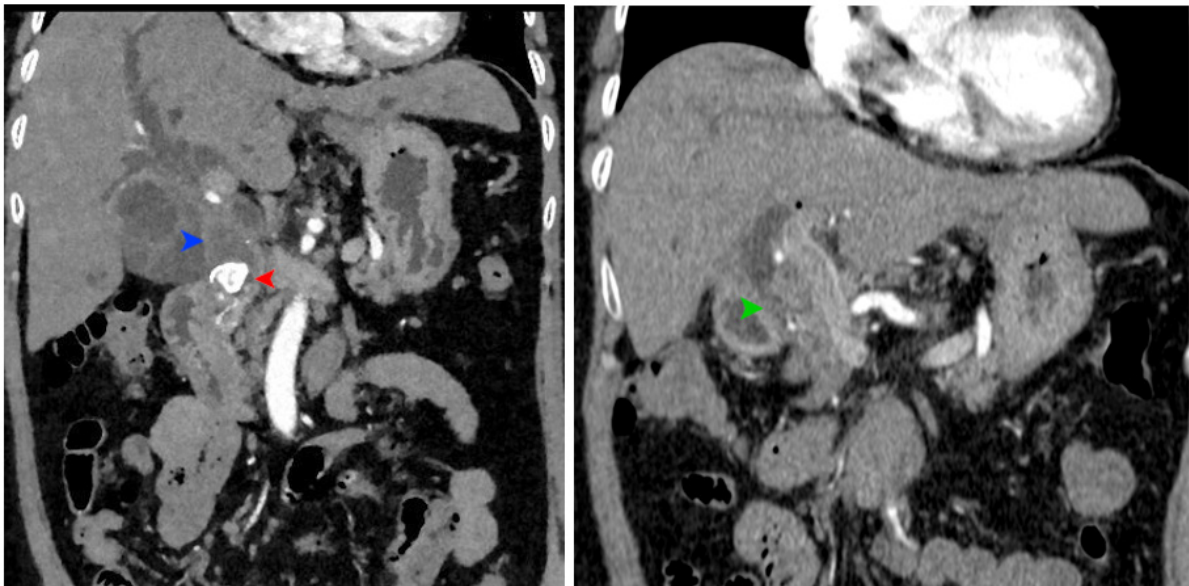
Chest X-Ray showed no sign of lung and skeletal metastasis. Abdominal MSCT showed bile stone in common bile duct causing dilatation of intrahepatic and extrahepatic bile duct, hydrops of gallbladder, and cholecystolithiasis. An intraductal mass was also observed proximal to the bile stone. There was no sign of tumor invasion on pancreas, portal veins or hepatic arteries, suggesting stage IIA Cholangiocarcinoma. Laboratory examination showed total bilirubin of 15.9 mg/dL, with direct bilirubin of 14.75 mg/dL.

Exploratory laparotomy was performed along with cholecystectomy and exploration of common bile duct. Most of the tumor was removed but there was still tumor residue. Choledochoduodenal shunt was created to allow direct bile drainage into duodenum. Five

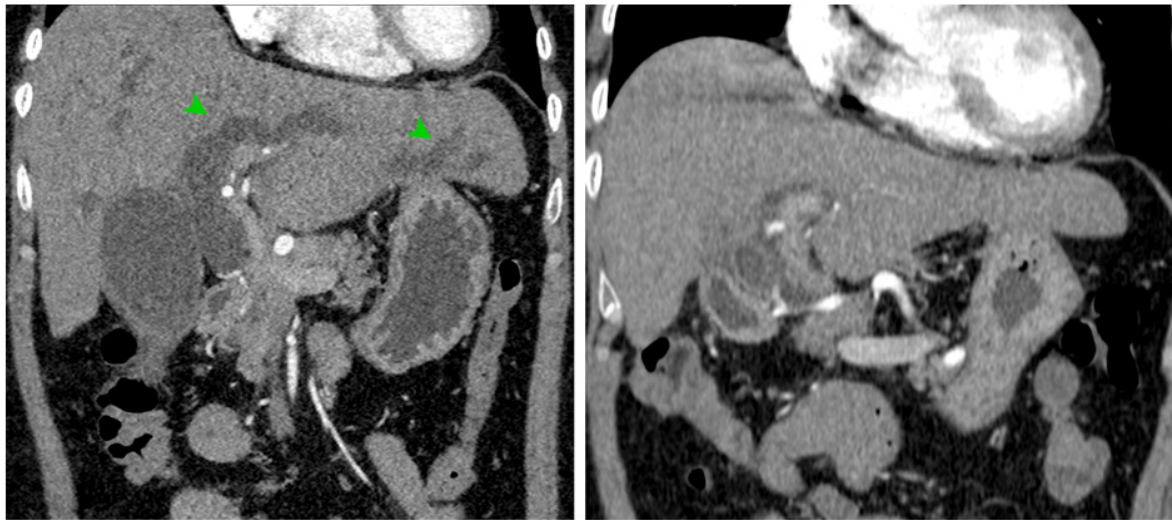
bile stones were found during surgery, two in gallbladder and three in common bile duct. Post-operative pathology showed mass in common bile duct and serous layer of gallbladder with histology of mucinous adenocarcinoma and signet ring cell carcinoma. The patient was discharged 12 days after surgery. Her symptoms improved upon discharge, although her jaundice remained. Her total bilirubin level on discharge was 6.01 mg/dL with direct bilirubin of 5.56 mg/dL. Chemotherapy was initiated three weeks post-surgery as complete tumor removal was not possible. The patient received six cycles of gemcitabine (1000 mg/m<sup>2</sup>, day 1 and 8) and cisplatin (70 mg/m<sup>2</sup>, day 1) every 3 weeks with tolerable side effect. CT-Scan was performed one month after the completion of chemotherapy which showed no sign of residual tumor.

## Discussion

Although some of CCA risk factors are well-understood, majority of CCA cases occur



**Figure 1.** Left: CT-Scan of the abdomen at diagnosis, showing bile stone (red arrow) in common bile duct with a mass lesion proximal to the stone (blue arrow). Right: CT-Scan performed 1-month post chemotherapy, showing no sign of residual tumor (green arrow).



**Figure 2.** Left: CT-Scan of the abdomen at diagnosis, showing dilatation of intrahepatic bile duct (green arrow). Right: CT-Scan performed 1-month post chemotherapy, showing no sign of bile duct dilatation.

sporadically. Some of established CCA risk factors include infection (HBV, HCV, liver flukes), chronic biliary tract inflammation (cholelithiasis, primary sclerosing cholangitis, liver cirrhosis, inflammatory bowel disease), congenital malformation (biliary-duct cysts) and toxins (thorium dioxide, smoking).<sup>1,3,4</sup> Some of CCA risk factors are thought to be geographically related, proven by variability of inter- and intra- continent incidence of CCA. Thailand, endemic area of *Opisthorchis viverrini* and *Clonorchis sinensis* infestation, has significantly higher prevalence of CCA compared to South East Asian countries in general (85/100,000 persons in northeastern Thailand compared to <2/100,000 persons in other south east Asian countries). Other endemic areas of liver fluke infestation such as China, Korea, and Japan also have higher prevalence of CCA (>2/100,000 persons).<sup>5</sup>

Most of CCA patients remain asymptomatic until the tumor mass is big enough to cause pain (intrahepatic) or obstruct biliary drainage system which

results in symptoms of obstructive jaundice (extrahepatic).<sup>6</sup> MRI and MRCP are considered to be the best modalities to detect and stage CCA.<sup>7</sup> CT-Scan is still widely used and is generally considered to provide acceptable but inferior result compared to MRI.<sup>8</sup>

Surgery is the mainstay treatment for CCA. Chemotherapy and radiotherapy are done in unresectable cases or when complete resection can't be achieved. The role of neoadjuvant chemotherapy and radiotherapy are limited as CCA is generally not sensitive to these modalities.<sup>9</sup> Should chemotherapy be prescribed, gemcitabine-based chemotherapy, either as single agent or in combination with other drugs, such as cisplatin, oxaliplatin, 5-FU, or capecitabine present as viable options.<sup>10</sup>

Adjuvant chemotherapy was prescribed for this patient since complete surgical removal of the tumor mass was not possible. Combination of gemcitabine and cisplatin was chosen as this regimen showed the best response in previous reports.<sup>11,12</sup> Liver transplant, the

best option for curative treatment, was not widely available in Indonesia thus was not an option for this patient. Before the initiation of chemotherapy, this patient's total bilirubin level was 6.01 mg/dL with direct bilirubin level of 5.56 mg/dL, traditionally classified as high risk for chemotherapy initiation.<sup>13</sup> We decided to go through with chemotherapy considering her excellent performance status. Furthermore, bilirubin level is not a reliable indicator of liver dysfunction severity in CCA patients, where the tumor mass might mechanically obstruct or constrict biliary ducts, resulting in obstructive jaundice.<sup>14</sup> A complete response was observed after four cycles of gemcitabine and cisplatin, which is in concordance with the relatively high response rate of this regimen in CCA as reported in previous studies.<sup>11,12</sup> This result is especially encouraging as Asian and Hispanic CCA patients are conventionally associated with worse prognosis.<sup>15</sup>

## Conclusion

Chemotherapeutic regimen of cisplatin and gemcitabine may offer safe treatment option for post-operative residual CCA patient presenting with hyperbilirubinemia.

## Acknowledgement

The authors express gratitude to Sardjito General Hospital for providing the necessary data for this publication.

## Declaration of Conflict of Interest

The authors have no conflict of interest to declare.

## Funding Acknowledgement

The authors received no financial support for the authorship and/or publication of this case report.

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