

# The Palliative Role of Colchicine on Advanced Hilar Cholangiocarcinoma Patient with Socio-Economic Challenges: A Case Report

Theo Audi Yanto<sup>1</sup>, Nathania Raphaeli Mulia<sup>2</sup>, Yordan Kusuma<sup>2</sup>

<sup>1</sup> *Department of Internal Medicine, Siloam Hospitals Lippo Village, Pelita Harapan University, Tangerang, Banten, Indonesia*

<sup>2</sup> *Faculty of Medicine, Pelita Harapan University, Tangerang, Banten, Indonesia*

## Abstract

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**Correspondance** : Theo Audi Yanto  
E-mail : [theo.audi@gmail.com](mailto:theo.audi@gmail.com)  
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Cholangiocarcinoma is a rare, slow-growing tumor that commonly presents beyond the point of resectability. Current guidelines recommend chemotherapy and radiotherapy for inoperable cases. However, palliative resources are not always accessible for patients with socio-economic barriers. Meanwhile, colchicine is a cost-effective drug and possesses anticancer effects. Here, we present a 53-year-old man with a 6-month history of painless jaundice, severe pruritus, recurrent fever, progressively growing abdominal mass, loss of appetite, and significant weight loss. He was incapable to perform adequate self-care and remained bedridden. Courvoisier sign was noted. Liver function tests show hyperbilirubinemia with elevated CA 19-9 level. Abdominal MRI 3T and MRCP showed hilar cholangiocarcinoma and obliteration of the hepatic vein. The patient and his family did not have health insurance and lived on a minimum income. Considered inoperable, the patient received daily colchicine 1 mg. Within four months, his symptoms have subsided, and he could perform several house chores. Bilirubin also showed a decreasing trend. In neoplastic cells, colchicine inhibits cell mitosis by perturbing tubulin formation. Being widely available, colchicine can be a palliative drug for terminally ill patients with socio-economic challenges. Although it improves patient performance status, we recommend further studies and close monitoring for the use of colchicine in advanced cholangiocarcinoma cases.

## Introduction

Half of cholangiocarcinoma cases are inoperable and thereby receive palliative care. Current treatment recommendations for inoperable cases, including chemotherapy and radiotherapy, are shown to produce poor results.<sup>1</sup> Despite the

advancement of research for palliative drugs, advanced cholangiocarcinoma patients often face social barriers to access these resources, leaving them with pain, discomfort, risk of developing cholangitis, and poor quality of life.<sup>2</sup> Meanwhile, colchicine, a cost-effective and widely

available anti-inflammatory drug for gout arthritis, was proven to have cytotoxic effects on cholangiocarcinoma cells.<sup>3</sup> Here, we present a case of a 53-year old man with advanced extrahepatic cholangiocarcinoma who received colchicine in his supportive care regimen.

### Case Illustration

A 53-year-old man presented with a 6-month history of painless jaundice, severe pruritus, recurrent fever, progressively growing abdominal mass at the right upper quadrant, loss of appetite, and significant weight loss. In the last 3 months, he experienced recurrent hospital admissions due to melena. He had not been able to perform self-care or other activities at home and almost remained bedridden. No other remarkable medical history except for excessive alcohol intake. On physical examination, he appeared to be alert and had icteric skin. Courvoisier sign, Terry's nail, and muscle atrophy were noted. The hematology panel shows normocytic normochromic anemia. Liver function test results were as follows: total bilirubin 27,31 mg/dL, direct bilirubin 26,24 mg/dL, ALP 1035 U/L, Gamma-GT 751 U/L, AST 124 U/L, ALT 164 U/L, CA 19-9 182 U/mL. Tests for autoimmune profile, hepatitis B and C were negative. Abdominal MRI 3T and MRCP showed hilar cholangiocarcinoma measuring around 3,3 x 4,8 x 1,7 cm at the fundus of the

gallbladder and 3,9 x 3,35 x 2,4 cm at the biliary bifurcation, extending towards proximal common bile duct and obliterated the portal vein. (Figure 1) Lymph nodes and other organs were within normal limits. The patient was referred to the digestive surgery department, and his condition was decided as an inoperable case.

The patient and his family were informed that he would undergo palliative care. While discussing the patient's further treatment plan, the family informed that they were not covered by the national health insurance and were living on minimum income. With limited palliative drugs in our hospital, he was given daily colchicine 1 mg, ursodeoxycholic acid 500 mg od, dexamethasone 0,5 mg tid, and curcumin 20 mg tid. He was assessed for his initial functional capacity before receiving further care with Functional Assessment Cancer Therapy – Hepatobiliary (FACT-Hep) questionnaires and received a total score of 91.

Four months later, his jaundice and cancer-related symptoms have subsided. At the same time, he was finally able to perform self-care and several house chores. Total bilirubin decreased to 1,01 mg/dL and direct bilirubin 0,91 mg/dL. His condition was assessed again with FACT-Hep questionnaires and received a total score of 140.

## Discussion

Biliary tract cancers are rare, slow-growing tumors comprised of less than 1% of all malignancy cases with a male-to-female ratio of 1.5:1.<sup>4</sup> Most cases are difficult to diagnose and are found in the advanced disease stage. Consequently, many patients can experience many delays in receiving early and adequate care.<sup>5</sup>

Cholangiocarcinomas are classified according to the origin of the tumor, whether from the biliary structure within the liver, referred to as intrahepatic cholangiocarcinoma, or outside the liver parenchyma, known as extrahepatic cholangiocarcinoma. Sixty to 70% of cases of extrahepatic cholangiocarcinoma arise from hilar structure, also known as Klatskin tumor.<sup>1</sup> Several risk factors are related to hilar cholangiocarcinoma, including advanced age, male gender, obesity, history of primary sclerosing cholangitis, cholelithiasis, parasitic infection, and alcohol intake.<sup>6</sup>

Clinical manifestation depends on tumor location. Patients with intrahepatic cholangiocarcinoma are initially asymptomatic and are often incidentally found during regular checkups.<sup>1</sup> Extrahepatic cholangiocarcinoma cases commonly present with signs and symptoms of the obstructive biliary tract, including painless jaundice, pruritus, dark urine, and pale stools.<sup>7</sup> Weight loss usually indicates advanced, unresectable disease.<sup>6</sup> Hyperbilirubinemia usually occurs,

accompanied by increased levels of alkaline phosphatase and gamma-glutamyl transferase in the state of cholestasis.<sup>8</sup> CA 19-9 is elevated in cholangiocarcinoma cases; however, it cannot be used for diagnostic purposes due to low sensitivity and specificity values.<sup>9</sup>

Diagnosing cholangiocarcinoma is best accompanied by imaging studies. Abdominal ultrasonography is handy to evaluate the local extend of disease and vascular involvement. However, the visualization result is operable-dependent. Assessment of liver parenchyma, lymph node involvement, and distant metastases would require other modalities such as computer tomography. Optimal visualization can be seen through magnetic resonance imaging in conjunction with magnetic resonance cholangiopancreatography to evaluate disease extension as it is non-invasive and highly accurate.<sup>9</sup>

Here, we present a case that matches the common description of an extrahepatic cholangiocarcinoma patient – a male patient that came with prolonged, obstructive jaundice and a history of excessive alcohol intake as a possible risk factor. Liver function panels showed hyperbilirubinemia, cholestatic state, and a high level of tumor marker (CA 19-9). Clinical presentation and laboratory workup were supported by the MRCP visualization of obstruction due to hilar cholangiocarcinoma at the fundus of the

gallbladder, biliary bifurcation, and proximal common bile duct with obliteration of the hepatic portal vein.

Surgery is the only curative treatment for cholangiocarcinoma, yet most cases present at an unresectable state.<sup>10,11</sup> Criteria for unresectable non-metastatic cholangiocarcinoma includes any of the following criteria: the patient is medically intolerant towards major operation, tumor extension to bilateral second-order biliary radicles, occlusion of the main portal vein, hepatic lobe atrophy with contralateral portal vein encasement or contralateral tumor extension to second-order biliary radicles, and proven metastases to lymph nodes, lung, liver, or peritoneum.<sup>12,13</sup>

This patient was not fit for surgery. Since he had difficulties in performing self-care and remained bedridden most of the time (ECOG Performance Status 3-4), he carried a higher risk of surgical complications. Furthermore, MRI/MRCP result showed the obliteration of the main portal vein, which limits the likelihood of vascular reconstruction.

Patients with unresectable cholangiocarcinoma are recommended to receive either palliative chemotherapy or radiotherapy.<sup>10</sup> Acknowledging his poor performance status and limited palliative modalities in our hospital, he did not have access to the recommended supportive care. The patient was the family's main source of income during his previously healthy state and retired early when he

experienced these symptoms. Hence, cost also becomes the main consideration for his medical care, including drugs, diagnostic work-ups, and the number of travels to the referral healthcare facility. He received colchicine 1 mg daily as an alternative, cost-effective, yet off-label supportive drug.

Colchicine is a natural alkaloid from plants called *Gloriosa superba*.<sup>3</sup> The highly available drug disrupts microtubule formation and cell mitotic process in a poorly reversible manner. Since neoplastic cells are recognized to have an abnormally increased rate of mitosis, colchicine has the potential to slow disease progression. The cytotoxic effects were studied in mice that carried cholangiocarcinoma. Cellular proliferation was significantly inhibited in a dose-dependent manner. Downregulation of proliferative genes, HSD11B2 and MT-COI, was observed. Lower levels of these genes impair cellular metabolism and thereby induces cell apoptosis. Tumor growth rates were also significantly lower, resulting in smaller tumor mass after 14 days of treatment compared with the control group.<sup>14</sup> Other proposed anticancer effects of colchicine include inhibition of metastatic potential and angiogenesis.<sup>15</sup>

To assess the effect of colchicine in this case, we used the Functional Assessment of Cancer Therapy (FACT-Hep) questionnaire that includes a set of questions regarding the symptoms and quality of life in hepatobiliary cancer

patients.<sup>16</sup> The total score ranges from 0 – 176. The higher the score determines the better quality of life. Our patient received a score of 91 on initial presentation and 140 after 4 months of consuming colchicine. Possibly, newly diagnosed patients have uncertainties towards their future which results in a lower score. If their therapy provides a favorable clinical response, the score increases during the second assessment.<sup>17</sup> Since our patient experienced fewer symptoms, has improved functional capacity (ECOG Performance Status 2), and a decreasing bilirubin trend showed up, colchicine possibly contributed to providing relief from obstructive jaundice due to cholangiocarcinoma.

Although colchicine is a promising palliative drug, we are concerned about its safety profile when consumed in a long-term period. Colchicine has a narrow therapeutic window. In absence of hepatic or renal impairment, 0.6 – 1 mg of colchicine daily can benefit terminal patients.<sup>14</sup> To the best of our knowledge, the toxic dose of colchicine has not been established globally. However, there have been reported cases of intoxication after consuming 7 mg of colchicine per day.<sup>18</sup> The initial manifestation of colchicine intoxication mostly includes gastrointestinal symptoms followed by multiple organ failures and life-threatening conditions. This condition is hardly recognized as

nausea and gastrointestinal upset are also common drug side effects. No antidote has ever been agreed upon if intoxication occurs. Since colchicine is rapidly distributed intracellularly, hemodialysis and plasma exchange are considered ineffective.<sup>19</sup>

## Conclusion

While most cholangiocarcinoma cases are not surgical candidates, access to the currently recommended palliative drug is not always available. Being widely available and affordable, colchicine can provide palliative effects for patients with inoperable cholangiocarcinoma. Since colchicine is still an off-label cancer drug, we recommend further studies and close monitoring when given to terminally ill patients.

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## Statement of Ethics

The subject of this case report has given his written consent to publish his case, including the publication of images.

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