



# Hyperbilirubinemia in gemcitabine plus nab-paclitaxel-treated patients with pancreatic cancer

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The mortality and mortality of pancreatic cancer is increasing in the world (1). It is the seventh leading cause of cancer-related death in the world, and the fifth among men and the third among women in Japan (1). Approximately 70–80% of pancreatic cancer patients are in an advanced stage with locally advanced and/or metastatic diseases at the time of diagnosis. Therefore, curative resection is possible for only 10–15% of patients. Even if the primary pancreatic cancer can be resected, the frequency of metastasis and recurrence is high, resulting in a 5-year survival rate below 10%. Furthermore, the survival of patients of unresectable pancreatic cancer is less than one year, even with chemotherapy (2). Therefore, to improve the patients' prognosis of advanced pancreatic cancer, the development of an effective and tolerable chemotherapy regimen is crucial. Gemcitabine (GEM) has become a universal standard chemotherapy for pancreatic cancer. Recently, GEM plus nab-paclitaxel (GnP) has shown better results than GEM alone in survival, and response rate.

Bilirubin is produced in the normal catabolic pathway by breakdown of hemoproteins. It is taken up from the plasma into the hepatocyte, and then it is conjugated to glucuronic acid. Then, the conjugated bilirubin is excreted into the bile duct. The upper limit of normal range of total bilirubin levels is 1.2 mg/dL. When the plasma level of bilirubin is elevated by 2–3-fold, jaundice can be detected. There are three categories of causes of an elevated serum bilirubin concentration. First, in prehepatic dysfunction, a high level of bilirubin is induced because of the breakdown of red blood cells and the liver is not able to

dissolve, for example, hemolysis, resulting in unconjugated hyperbilirubinemia. Second, intrahepatic dysfunction, induced by liver damage or intrahepatic biliary obstruction caused by hepatotoxic drugs, and posthepatic obstruction of the biliary passage, both predominantly result in conjugated hyperbilirubinemia. Stones in the common bile duct and cancer of the head of the pancreas often cause biliary obstructions. Hyperbilirubinemia is often both in diagnosis and during the development of pancreatic cancer. Approximately 70–80% of pancreatic cancer patients have hyperbilirubinemia caused by obstruction of the common bile duct (3). To choose the appropriate treatment for the hyperbilirubinemia patients, it is important to distinguish whether it is caused by the tumor, and whether it is curable or not.

Biliary obstruction and hyperbilirubinemia increase the risk of cholangitis and cause frequent hospitalization, which complicates the treatment of patients. Therefore, hyperbilirubinemia is associated with poor prognosis in patients with pancreatic cancer. In addition, obstruction of the peripheral intrahepatic bile ducts by tumor metastases often causes hyperbilirubinemia without massive infiltration of the liver metastasis of tumor, resulting in non-cirrhotic liver failure. We need to distinguish between causes of obstruction, parenchymal failure by liver metastasis, previous liver disease, and other cases.

Liver failure in pancreatic cancer patients may influence on the pharmacokinetic properties of drugs. Decrease of metabolic capacity of the liver, in relation to cytochrome P450 (CYP450), alter hepatic drug metabolism. A heme-

iron center in the active site of CYP450 plays a key role in the drug metabolism, accounting for approximately 75% of the total metabolism. Depending on the metabolism, this may not only lead to impaired biological activity of a pro-drug but also impaired inactivation of the drug. Obstruction of the common bile duct causes the failure of drug excretion through the bile. Portal vein thrombosis caused by a hypercoagulability or vascular endothelial injury, which reduced blood supply to the liver and lead to increased pressure in the portal vein system, thus affecting drug metabolism. Therefore, interfering with the pharmacokinetics of hepatic insufficiency patients lead to decreased efficacy or increased toxicity of the chemotherapeutic agents.

Hyperbilirubinemia is an important factor in deciding treatment interruption; the others are high fever, severe nausea, or pancytopenia during chemotherapy. Hyperbilirubinemia is an exclusion criterion in most clinical studies of the chemotherapy commonly used in pancreatic cancer. Treatment strategies for patients with hyperbilirubinemia are based on small sample size of phase I and published studies (4). Most phase I, II, and III studies have kept out patients with abnormal serum liver biochemical tests, including high level of bilirubin; therefore, a large number of patients may be excluded from potentially beneficial treatment. Consequently, our understanding of the optimal starting doses of chemotherapy for these individuals is very limited. Apart from individual reports, there are no evidence from clinical studies to recommend GnP treatment in patients with pancreatic cancer and hyperbilirubinemia. Therefore, treatment with GnP is not recommended in pancreatic cancer patients who have moderate to severe hepatic impairment, as there is not enough evidence to indicate dosage recommendations.

Rogers *et al.* performed a retrospective analysis and reported a modified-dose GnP in 12 patients with advanced pancreatic cancer with baseline hyperbilirubinemia (2.1–5.2 mg/dL) (5). They found that the reduced GnP (NabP 100 mg/m<sup>2</sup> and GEM 600 mg/m<sup>2</sup> at a fixed dose rate of 10 mg/m<sup>2</sup>/minute, given either biweekly or weekly for 3 weeks followed by 1 week off) was well tolerated. In addition, neutropenia, thrombocytopenia, and fatigue were important predictors of dose delay that may be useful when making treatment decisions. Similarly, Pelzer *et al.* showed that GnP administration in 29 patients with an elevated bilirubin level (total bilirubin  $\geq$ 1.2 mg/dL) did

not show unexpected side effects assessed by predefined (non-) hematological parameters (6). They divided patients into three groups based on their bilirubin level (A, 1.2–3 mg/dL; B, >3–5 mg/dL; C, >5 mg/dL) and found that overall survival from the first treatment of GnP did not show any difference between the groups. These findings indicate that GnP administration in patients suffering from advanced pancreatic cancer with cholestatic hyperbilirubinemia was safe and feasible with regard to individualized dose administrations. A multicenter trial in patients with hyperbilirubinemia is needed to confirm these findings in a prospective setting.

The sources of obstructive, the advisable treatment for hyperbilirubinemia is eliminated by endoscopic biliary drainage. Biliary decompression in patients followed obstructive hyperbilirubinemia is normally executed treating an endoscopic biliary stent placement, which had lower mortality and assisted treatment with chemotherapy by decreasing bilirubin to 1.5–2 times the normal limit of the reference range value. However, the utility of biliary drainage using stents remains controversial. van der Gaag *et al.* reported that preoperative biliary drainage increased complications and did not improve survival; thus, they concluded that preoperative biliary drainage might not be recommended (7). However, Kubota *et al.* reported that a self-expandable metal stent allowed for safe neoadjuvant chemoradiation in patients with a borderline resectable pancreatic head cancer (8). While these reports indicated safety and efficacy for patients with pancreatic cancer who have hyperbilirubinemia utilizing GnP, further prospective studies are needed to establish treatment strategies for hyperbilirubinemia in the setting of chemotherapy.

Paclitaxel and gemcitabine have two different metabolic pathways, making pharmacokinetic interactions unexpected (9). Pay close attention to changes in liver baseline values during treatment with gemcitabine is recommended. Treatments should be individualized for each patient according to the performance status, previous comorbidities, and current and foreseeable blood bilirubin levels. The main limitations of previous clinical studies are the large heterogeneity and small sample sizes, particularly with regard to the etiology and degree of hepatic impairment. Larger clinical studies with GnP, especially in neoadjuvant and adjuvant settings, in pancreatic cancer patients who have hyperbilirubinemia caused by the bile duct obstruction will hopefully further clarify the efficacy of hyperbilirubinemia on the visible effects and confidence of GnP.

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