MINI-REVIEW

Benefits of Metformin Use for Cholangiocarcinoma

Soraya J Kaewpitoon1,2,3,*, Ryan A Loyd1,3, Ratana Rujirakul3, Sukij Panpimanmas3,4, Likit Matrakool3,4, Taweesak Tongtawee3,4, Nusorn Kootanavanichpong5, Ponthip Kompor5, Wasugree Chavengkun5, Jirawoot Kujapun5, Jun Norkaew5, Sukanya Ponphimai5, Natnapa Padchasuwan6, Poowadol Pholsrpradit7, Thawatchai Eksantit, Tanida Phatisena8, Natthawut Kaewpitoon2,3,5

Abstract

Metformin is an oral anti-hyperglycemic agent, which is the most commonly prescribed medication in the treatment of type-2 diabetes mellitus. It is purportedly associated with a reduced risk for various cancers, mainly exerting anti-proliferation effects on various human cancer cell types, such as pancreas, prostate, breast, stomach and liver. This mini-review highlights the risk and benefit of metformin used for cholangiocarcinoma (CCA) prevention and therapy. The results indicated metformin might be a quite promising strategy CCA prevention and treatment, one mechanism being inhibition of CCA tumor growth by cell cycle arrest in both in vitro and in vivo. The AMPK/mTORC1 pathway in intrahepatic CCA cells is targeted by metformin. Furthermore, metformin inhibited CCA tumor growth via the regulation of Drosha-mediated expression of multiple carcinogenic miRNAs. The use of metformin seems to be safe in patients with cirrhosis, and provides a survival benefit. Once hepatic malignancies are already established, metformin does not offer any therapeutic potential. Clinical trials and epidemiological studies of the benefit of metformin use for CCA should be conducted. To date, whether metformin as a prospective chemotherapeutic for CCA is still questionable and waits further attention.

Keywords: Metformin - cholangiocarcinoma - bile duct cancer - gall bladder cancer

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Introduction

Cholangiocarcinoma (CCA) is neoplasms that involve the epithelial cells of the bile duct, also known as one of the most aggressive malignant tumors associated with local invasiveness and a high rate of metastasis. CCA is originated in the bile duct in which drained bile from the liver into the small intestine. Other biliary tract cancers include pancreatic cancer, gall bladder cancer, and cancer of the ampulla of Vater. It is also known to be one of the most common causes of cancer related death in Thailand and it has been reported that Thailand is the highest incident of the world (Green et al., 1991; Sripa et al., 2007; Shin et al., 2010). It has an annual incidence rate of 1-2 cases per 100,000 in the Western world, but rates of CCA have been rising worldwide over the past several decades (Landis et al., 1998; Patel, 2002).

This disease is difficult to diagnose early, as most symptoms present late in the disease. In addition, the specific anatomic position can cause periductal extension and result in a very low radical excision rate and a very poor prognosis. Furthermore, CCA is considered to be an incurable and rapidly lethal disease unless all the tumors can be fully resected. Three-year survival rates of 35% to 50% are achieved only in a subset of patients who have negative histological margins at the time of surgery (Akamatsu et al., 2011). Survival of CCA patients in northeastern Thailand after supportive treatment was reported and indicated that the stage of disease was an important prognosis factor affecting survival of CCA patients who had diagnosis in late stage. The encourage patients to see health personnel at early stage is very important (Thunyaharn et al., 2013). Palliative therapeutic approaches, consisting of percutaneous and endoscopic biliary drainage, have usually been used for these patients because there is no effective chemotherapeutic treatment for this type of cancer.

Chemotherapy agents used to treat CCA include 5-fluorouracil with leucovorin (Choi et al., 2000), gemcitabine and irinotecan (Bhargava et al., 2003), combining gemcitabine and capecitabine (Knox et al, 2005), gemcitabine as a single agent (Park et al., 2005), or
A number of risk factors for the development of CCA have been described. Multifactorial is associated to develop CCA. The 3 main factors have been hypothesized, including carcinogen agents, infection, and other factors. Caroli’s disease, cholecodocal cyst, liver fluke infection, gallstones, hepatotholithiasis, sclerosing cholangitis, thorotrac, and ulcerative colitis, are strongly associated with CCA development. While, Asbestos, isoniazid, methyldopa, oral contraceptive, polychlorinated biphenyls are the possibly associated to develop CCA. The most common of these is primary sclerosing cholangitis and an inflammatory disease of the bile ducts which is itself closely associated with ulcerative colitis (Chapman, 1999). Alcoholic liver disease, or cirrhosis of the liver due to other causes, are at significantly increased risk of CCA (Sorensen et al., 1990; Sripa et al., 2005). The presence of hepatitis, intrahepatic stones, which is rare in the West, but common in parts of Asia, has been strongly associated with CCA (Su et al., 1997; Donato et al., 2001; Lee et al., 2002). Caroli’s syndrome or choledocal cysts, congenital liver abnormalities, have been associated with an approximately 15% lifetime risk of developing CCA (Dayton et al., 1983; Lipsett et al., 1994). The rare inherited disorders Lynch syndrome II has also been found to be associated with CCA (Mecklin et al., 1992; Lee et al., 2004). Carcinogens have been described that are the main factor to develop CCA. Exposure to Thorotrat has been linked to the development of CCA as late as 30-40 years after exposure; Thorotrat was banned in the United States in the 1950s due to its carcinogenicity (Sahani et al., 2003; Zhu et al., 2004). Dimethylnitrosamine is the caused of primary carcinoma and could induced CCA development in both animal model and human epidemic data. Nitrates and nitrites were found in local Thai preserved protein foods that strongly positive associated to develop CCA (Herrold 1967; Migasena and Changbunrung, 1974; Migasena et al., 1980).

Infections are associated with the development of CCA, mainly liver flukes, *Opisthorchis viverrini* (Watanapa and Watanapa, 2002; Sripa et al., 2007; Kaewpitoon et al., 2008; Sripa et al., 2010), *O. felineus* (Maksimova et al., 2015), *Clonorchis sinensis* (Hong and Fang, 2012; Rustagi and Dasanu, 2012), and viral hepatitis (e.g. hepatitis B or hepatitis C) (Kobayashi et al., 2000; Lu et al., 2000; Yamamoto et al., 2004). In Thailand, the experimental and epidemiological evidences strongly indicated that *O. viverrini* infection in the etiology of CCA (Thamavit et al., 1978; IARC, 1994; Sripa et al., 2007). There has been a strong, positive correlation between opisthorchiasis-associated CCA and infection with *Helicobacter*. Infection with *H. bilis* and *H. hepaticus* species can cause biliary cancer (Chang and Parsonnet, 2010). Other factors are associated with CCA development, mainly smoking (Mitacek et al., 1999), obesity, and diabetes mellitus (DM) (Saengboonmee et al., 2015). The data from several epidemiological studies strongly indicate that DM is a risk factor of both intrahepatic and extrahepatic CCA, including gall bladder cancer (Ren et al., 2011; Jing et al., 2012; Palmer and Patel, 2012; Zhang et al., 2013). There is no epidemiological study of the association of DM and *O. viverrini* associated CCA in Thailand. However, the association of DM and CCA in Thailand, has been reported by Saengboonmee et al. (2015) that almost all provinces with a high mortality rate of DM also had a high mortality rate of liver and biliary tract cancer.
cancers, mainly the anti-proliferation effect on various human cancer cell types, such as pancreas (Akinuye et al., 2013), prostate (Nair et al., 2013), breast (Alimova et al., 2009), stomach (Kato et al., 2012) and liver (Petrushev et al., 2012).

Many studies have been reported that metformin might be a quite promising strategy for CCA prevention and treatment. Presently, Bhat et al. (2013) reveal that metformin, which represses mechanistic/mammalian target of rapamycin (mTOR) signaling, the mTOR pathway plays a critical role in cellular metabolism, growth, and proliferation and has been evaluated as a target for therapy in various malignancies. The mTOR pathway is a major tumor-initiating pathway in hepatocellular carcinoma, with up-regulation seen in up to 50% of tumors, by activating adenosine monophosphate-activated protein kinase, has been shown to decrease liver carcinogenesis in population studies. There is also evidence of mTOR pathway activation in CCA, although its biological significance in initiating and promoting tumor progression remains ambiguous. Meanwhile, Jiang et al. (2015) have been reported that metformin inhibited CCA tumor growth by cell cycle arrest in vitro and in vivo. The expression of six miRNAs (mir124, 182, 27b, let7b, 221 and 181a), which could directly target cell-cycle-regulatory genes, was altered by metformin in vitro and in vivo. These miRNAs were dysregulated in CCA and promoted the CCA genesis and metformin exactly modulated these carcinogenic miRNAs expression to arrest the cell cycle and inhibit the proliferation. These miRNAs expression changes correlated with the tumor volume and postoperative survival of CCA patients and could be used to predict the prognosis. This study indicated that metformin inhibited CCA tumor growth via the regulation of Drosha-mediated multiple carcinogenic miRNAs expression and comprehensive evaluation of these miRNAs expression could be more efficient to predict the prognosis. This study also indicated that metformin inhibited CCA tumor growth through the regulation of Drosha-mediated multiple carcinogenic miRNAs expression and comprehensive evaluation of these miRNAs expression could be more efficient to predict the prognosis. This study suggested that metformin exerts a chemotherapeutic effect on cancer by reducing cell proliferation and inducing cell cycle arrest and apoptosis. However, metformin did not improve the survival of CCA patients with DM. Santos et al. (2012) has been reported a 56-year-old woman was admitted with jaundice, and laboratory data were indicative of pancreatitis, which recurred in spite of adequate clinical and nutritional management. The patient was an overweight diabetic using metformin, who had antecedents of cholelithiasis and recent cholecystectomy. The histopathology study of the transpapillary biopsy confirmed the ampullary adenocarcinoma.

Conclusion

That metformin decreased the risk of CCA as chemoprevention is clearly demonstrated in many studies, however, the argument of metformin did not improve the survival of CCA patients with DM is described. Therefore, The clinical trial and epidemiological studies the benefit of metformin use for CCA should be more investigated. To date, whether metformin as a prospective chemotherapeutic CCA is still questionable and is waiting for discovery.

References

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