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Chemoresistance in Patients with Resected Locally Advanced Lymph Node-Positive Colon Cancer and Poorly Controlled T2DM: What Relationship?

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ABSTRACT

Colon cancer (CC) ranks among the most common cancers globally, with its occurrence steadily rising in numerous countries. However, advancements in diagnostic methods, monitoring techniques, and surgical procedures have led to significant progress. Adjuvant chemotherapy is the standard treatment for patients with resected, locally advanced, lymph node-positive (stage III) colon cancer. Type II diabetes mellitus (T2DM) is a metabolic condition marked by chronic hyperglycemia. Research into the link between T2DM and cancer has significantly increased since T2DM was identified as a major risk factor for gastrointestinal diseases and various cancers, including pancreatic, breast, and colorectal cancer (CRC). Future research should prioritize investigating the underlying mechanisms connecting hyperglycemia and lifestyle factors to postoperative chemoresistance in patients with colon cancer (CC).

Keywords: Colon Cancer; Chemoresistance; Diabetes Mellitus; Prognosis; Type II Diabetes Mellitus

Abbreviations: CC: Colon Cancer; CRC: Colorectal Cancer; CRR: Chemotherapy Resistance Rate; FPG: Fasting Plasma Glucose; BMI: Body Mass Index; CRA: Colorectal Adenoma

Core Tip

In this editorial, we comment on a Retrospective Cohort Study by Guan RY et al published in the recent issue of the World Journal of Gastroenterology. The authors of this article aimed to highlight that poorly controlled preoperative hyperglycemia is linked to increased chemoresistance and a poorer prognosis in patients undergoing surgery for stage III colon cancer. The same study emphasized the significance of managing hyperglycemia in patients with type 2 diabetes mellitus (T2DM) and suggested that glycemic parameters, such as fasting plasma glucose and glycosylated hemoglobin levels, could serve as potential predictive indicators for chemotherapy responses.

Introduction

Colon cancer (CC) ranks among the most common cancers globally, with its occurrence steadily rising in numerous countries. However, advancements in diagnostic methods, monitoring techniques, and surgical procedures have led to significant progress. Over recent decades, the incidence rate of CC per 100,000 individuals has declined from 60.5 to 38.7, while the 5-year relative survival rate has increased from 50% to 65%. Regardless of these advancements, tumor recurrence occurs in approximately 20%-30% of patients following surgery, presenting significant challenges for colon cancer treatment and limiting the overall effectiveness of therapies [1,2].

Chemotherapy

Adjuvant chemotherapy is the standard treatment for patients with resected, locally advanced, lymph node-positive (stage III) colon cancer. Currently, chemotherapy regimens that include oxaliplatin and/or fluoropyrimidines are widely recognized for enhancing postoperative outcomes in CC patients [3,4]. Capecitabine, an oral prodrug of 5-fluorouracil, is a fluoropyrimidine utilized in the treatment of colon cancer across both early and advanced stages. It can be

administered as monotherapy or in combination with other chemotherapeutic agents. Capecitabine offers a more convenient treatment regimen compared to intravenous 5-fluorouracil, with notably fewer side effects such as diarrhea, nausea, and stomatitis. However, the advantages of capecitabine-based therapy are often undermined by the onset of chemoresistance, which can result in tumor recurrence and metastasis [5,6]. These findings indicate that further in-depth studies are necessary to identify effective strategies for overcoming or reducing chemoresistance following surgical resection.

Type II Diabetes Mellitus (T2DM)

Type II diabetes mellitus (T2DM) is a metabolic condition marked by chronic hyperglycemia. Research into the link between T2DM and cancer has significantly increased since T2DM was identified as a major risk factor for gastrointestinal diseases and various cancers, including pancreatic, breast, and colorectal cancer (CRC). Prolonged hyperglycemia contributes to tumor progression, cancer cell proliferation, and metastasis [7,8]. Additionally, antidiabetic medications like metformin have demonstrated anticancer properties and the ability to improve chemotherapy sensitivity in cancers such as ovarian, lung, and acute myeloid leukemia. Metabolic disorders are considered key characteristics of cancer [9,10]. Importantly, certain genetic drivers of colon cancer, such as P53, KRAS, and Wnt, have been identified as regulators of cancer metabolism. This suggests that metabolic disorders may play a significant role in the carcinogenesis of colon cancer [11,12]. The impact of type 2 diabetes mellitus (T2DM) on colon cancer (CC) has been widely debated, with studies indicating that T2DM elevates the risk of developing CC. Furthermore, metformin, whether used alone or in combination with chemotherapy, shows promise as a potential therapeutic agent for inhibiting cancer progression and overcoming chemoresistance, as demonstrated in vitro and animal studies [13,14]. Given this evidence, it is reasonable to speculate that hyperglycemia may contribute to chemoresistance in patients with colon cancer following surgical resection.

The study by Guan RY et al. found that elevated preoperative fasting plasma glucose (FPG) and HbA1c levels, rather than a history of type 2 diabetes mellitus (T2DM), were strongly associated with a higher chemotherapy resistance rate (CRR) and poorer postoperative prognosis in patients who underwent curative surgery for stage III colon cancer and started capecitabine treatment afterward. These findings suggest that poorly controlled type 2 diabetes mellitus (T2DM) is a risk factor linked to worse postoperative outcomes. Previous studies have indicated a strong relationship between hyperglycemia and the onset and progression of colon cancer. The study by Guan RY et al. further confirms that poorly controlled T2DM is an independent risk factor associated with postoperative chemoresistance [15-17]. Type II diabetes mellitus (T2DM) has consistently been linked to an increased risk of developing colon cancer (CC) in clinical cohort studies. The primary characteristics of T2DM are hyperglycemia and impaired glucose metabolism. Additionally, tumor cells have a glycolytic rate up to 200 times higher than that of normal cells. The elevated plasma glucose levels in diabetic patients provide ample energy for the growth of CC cells, potentially promoting tumor progression, recurrence, metastasis, and even chemoresistance in individuals with both CC and T2DM [18].

Patients with type 2 diabetes mellitus (T2DM), particularly those in the early stages without complications such as retinopathy, diabetic nephropathy, diabetic foot disease, cerebrovascular disease, or recurrent hypoglycemia, often exhibit higher serum insulin levels. Studies have shown that insulin, by binding to the insulin-like growth factor receptor-1, activates downstream signaling pathways that promote cellular proliferation and protein synthesis in tumor cells [19,20]. The study by Yang IP et al. indicated that blood sugar levels, rather than a history of diabetes mellitus, can enhance oxaliplatin chemoresistance, which aligns with our findings.

Lifestyle and Postoperative Outcomes

Lifestyle factors such as body mass index (BMI), smoking, and alcohol abuse are well-established risk factors for gastrointestinal carcinogenesis [21]. Dinas PC et al. concluded that combining physical activity or exercise with dietary and nutritional interventions can lead to multiple health benefits for cancer patients and survivors. These include reductions in body weight, fat mass, insulin levels, and inflammation, as well as improvements in lipid profiles, physical quality of life, and symptoms of depression [22]. Yang, L et al. demonstrated the comprehensive advantages of physical activity in managing and controlling cancer [23]. Yu J et al. concluded that embracing a greater number of healthy lifestyle practices is linked to a reduced risk of colorectal cancer (CRC), colorectal adenoma (CRA), and CRC-specific mortality. Encouraging the adoption of healthy lifestyles could significantly alleviate the burden of CRC [24]. Furthermore, Amirsasan R et al. demonstrated that exercise serves as an effective post-treatment management strategy for colorectal cancer survivors. It enhances muscle strength, cardiorespiratory fitness, and physical activity levels, while also reducing emotional distress, fatigue, and improving sleep quality in patients undergoing chemotherapy [25]. Finally, Ligibel JA et al. recommended that oncology providers should encourage patients to engage in regular aerobic and resistance exercise during active treatment with curative intent.

Conclusion

Patients with type 2 diabetes mellitus (T2DM) who underwent surgical resection for stage III colon cancer (CC) experienced significantly increased postoperative chemoresistance and poorer long-term outcomes when their preoperative hyperglycemia was poorly controlled. Combining physical activity or exercise with dietary and nutritional interventions can lead to multiple health benefits for cancer patients and survivors. Future research should prioritize investigating the underlying mechanisms connecting hyperglycemia and lifestyle factors to postoperative chemoresistance in patients with colon cancer (CC).

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