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Circulating tumor cells as prognostic marker in pancreatic cancer

Melek Yakar, Durmuş Etiz

Abstract

In this editorial we comment on the article by Zhang *et al* published in the recent issue of the *World Journal of Clinical Oncology*. Pancreatic cancer is the fourth most common cause of cancer-related mortality and has the lowest survival rate among all solid cancers. It causes 227,000 deaths annually worldwide, and the 5-year survival rate is very low due to early metastasis, which is 4.6%. Cancer survival increases with better knowledge of risk factors and early and accurate diagnosis. Circulating tumor cells (CTCs) are tumor cells that intravasate from the primary tumor or metastasis foci into the peripheral blood circulation system spontaneously or during surgical operations. Detection of CTC in blood is promising for early diagnosis. In addition, studies have associated high CTC levels with a more advanced stage, and more intensive treatments should be considered in cases with high CTC. In tumors that are considered radiologically resectable, it may be of critical importance in detecting occult metastases and preventing unnecessary surgeries.

INTRODUCTION

Pancreatic cancer is the fourth most common cause of cancer-related mortality and has the lowest survival rate among all solid cancers[1]. It causes 227000 deaths annually worldwide, and the 5-year survival rate is very low due to early metastasis, which is 4.6%[2]. Survival rates increase with better recognition of risk factors, early and accurate diagnosis, and timely administration of the correct treatment. Surgery is essential for

curative treatment in pancreatic cancer, but the rate of patients with resectable tumors is quite low[3]. Distant metastases are present in half of the patients at initial presentation, and 20%-30% of patients have an unsectable locally advanced tumor. Unfortunately, only 15%-20% of patients diagnosed with pancreatic cancer are considered operable. In operable patients suitable for radical excision, 5-year survival rates vary between 20%-25%[4].

Since there is no standard general population screening, the majority of patients are diagnosed after symptomatic findings. Initial symptoms such as malaise, fatigue, loss of appetite, and weight loss are often nonspecific. Jaundice associated with pancreatic cancer is the initial symptom in only 12% of patients, while jaundice develops during the course of the disease in 50% of patients. New-onset diabetes may be the first sign of pancreatic cancer. Some factors, such as tumor size, node and metastasis stage, and lymph node metastasis, affect treatment response. Although serum carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) levels play a helpful role in the diagnosis of pancreas, they are insufficient to predict prognosis[5]. The usefulness of biomarkers such as CA19-9 and CEA, which are commonly used in early diagnosis, is highly variable among patients[6]. New diabetes due to pancreatic cancer usually affects older patients. Sharma *et al*[7] have created an automated algorithm that uses age, weight, and blood sugar changes to select high-risk patients for pancreatic cancer screening programs. A randomized trial evaluating this algorithm is ongoing[8].

Circulating tumor cells (CTCs) are tumor cells that intravasate from the primary tumor or metastasis foci into the peripheral blood circulation system spontaneously or during surgical operations. CTCs were first discovered in 1896 and to this day have an important place in precision medicine such as cancer biology, molecular profiling and tumor liquid biopsy[9]. CTCs are also being investigated for more accurate prognosis predictions in pancreatic cancer.

CIRCULATING TUMOR CELLS IN PANCREATIC CANCER

CTCs are tumor cells that can enter the blood circulation system. This cellular population, along with tumor-derived new vessels, circulates through the peripancreatic vessels and their capillaries, ultimately causing metastasis in many organs. CTCs can enter the bloodstream in two ways: They are released by passive shedding from the tumor surface or through an active epithelial-mesenchymal transition mechanism. Many tumor cells are shed at the early stage of tumorigenesis *via* the primary mechanism[10]. Achieving R0 resection in pancreatic cancer is very important in the treatment of early stage localized tumors. The amount of CTCs detected in the blood before treatment may be important in making treatment-related decisions. For example, surgery without neoadjuvant treatment can be applied to patients with a low preoperative CTC burden compared to patients with a high CTC burden[11]. Identification of CTCs and differentiation of their subgroups during the treatment process may be useful in the early detection of conditions such as tumor metastasis and chemotherapy resistance[12]. In a study conducted by Okubo *et al*[13] with 40 patients diagnosed with locally advanced stage unsectable pancreatic cancer, they evaluated CTCs before and after treatment. The incidence of CTC positivity in the first three months from the start of treatments in patients with progressive and stable disease or partial response was 45.4% and 24.1%, respectively. The overall survival rate was significantly lower in patients with CTC than in patients without CTC ($P = 0.045$). To reduce the invasive examination of metastatic lesions, "liquid biopsy" of CTCs representing metastatic lesions may be a good option for diagnosis and subsequent treatment. If mutation in CTCs can be detected, resistance to treatment can be evaluated in real time[14]. In a retrospective study conducted by Tan *et al*[15], 155 patients receiving anti PD-1 immunotherapy were evaluated, and 6 out of 155 cases were advanced stage pancreatic cancer. While the disease control rate is 71% in the group of PDL1-positive CTCs, the disease control rate in the remaining cases is only 39%. In their study with 100 patients, Wei *et al*[16] examined CTC levels in peripheral blood and found positive in 76% of the patients. The decrease in follow-up CTC values during chemotherapy has been associated with response to chemotherapy.

Apart from diagnosis or treatment decision, CTCs have also been used in prognosis evaluation in pancreatic cancer.

In a study conducted by Kulemann *et al*[17], CTC was investigated in blood samples taken from healthy donors diagnosed with pancreatic cancer. While CTC positivity was detected in 11 patients (73%) diagnosed with pancreatic cancer, CTC was not detected in any of the 9 donors. According to this study, circulating tumor cells can be found in most patients with pancreatic cancer in localized, locally advanced, or metastatic disease.

In the study conducted by Gao *et al*[18] with 25 cases diagnosed with pancreatic cancer (including 5 stage I, 8 stage II, 6 stage III and 6 stage IV), CTC was studied from peripheral blood samples, and high CTC count was found to be associated with poor overall survival. According to this study, sensitivity and specificity in diagnosis with CTC are 88% and 90%. When CTC level and CA19-9 level are combined, the detection rate of pancreatic cancer can be 100%. Moreover, higher levels of CTCs successfully predict unfavorable prognosis.

In a study conducted by Court *et al*[19] with 126 patients (100 cancer, 26 benign disease), CTC was studied from venous blood samples. In this study, CTC was detected in 78% of patients diagnosed with pancreatic cancer, and as the stage progressed, the CTC level was also found to increase. In other words, a direct proportion was determined between CTC count and advanced stage. Occult metastases were detected during surgery in 13 of 53 patients who were planned for potentially curative surgery. Patients with occult metastases have statistically significantly more CTCs than patients with local disease. According to this study, CTC can determine prognosis. Additionally, CTCs show potential as a preoperative biomarker in identifying patients at high risk for occult metastatic disease.

In a study conducted by Effenberger *et al*[20] with 23 patients diagnosed with pancreatic cancer, it was revealed that CTC affected both progression-free survival and overall survival.

Studies on CTCs in pancreatic cancer have found that CTCs are associated with 1-year disease recurrence and mortality, progression-free survival and overall survival[21-23].

Diagnosis with CTC is a non-invasive procedure, does not require hospitalization, and the probability of complications is much lower than biopsy. It also has high sensitivity and specificity in diagnosis. The patient's comfort, unnecessary hospitalization time and costs will be eliminated if the diagnosis can be made with CTC. It can also provide practical guidance for treatment selection.

CONCLUSION

There is no screening test for pancreatic cancer today, and life expectancy in cases that are generally locally advanced or metastatic at the time of diagnosis is short despite treatments. Detection of CTC in blood is promising for early diagnosis. In addition, studies have associated high CTC levels with a more advanced stage, and more intensive treatments should be considered in cases with high CTC. In tumors that are considered radiologically resectable, it may be of critical importance in detecting occult metastases and preventing unnecessary surgeries.

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