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ScienceDirect

EJSO the Journal of Cancer Surgery

EJSO xx (2017) 1–7 www.ejso.com

The metastasis status and tumor burden-associated CA125 level combined with the CD4/CD8 ratio predicts the prognosis of patients with advanced pancreatic cancer: A new scoring system

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Accepted 14 July 2017
Available online ■ ■ ■

Abstract

Introduction: Although CA125 and the tumor immune response have been reported to be associated with pancreatic cancer, their prognostic value for advanced pancreatic cancer patients undergoing chemotherapy remain uncertain. We thus studied the prognostic value of the combination of the CA125 level with the CD4/CD8 ratio.

Methods: After excluding patients who were lost to follow-up or for whom complete clinical data were missing, 369 participants were ultimately examined. Univariate and multivariate analyses were performed using the Cox hazards model, and Kaplan–Meier methods and log-rank tests were used for the comparison of survival rates.

Results: Univariate and multivariate analyses showed that a high CA125 level and a high CD4/CD8 ratio were independent prognostic factors (CA125 $\geq$ 35 U/ml, Hazard Ratio (HR) = 1.90, $p < 0.001$; CD4/CD8 $\geq$ 1.8, HR = 1.37, $p = 0.004$). Moreover, after combining the CA125 level and CD4/CD8 ratio to form a new scoring system, the HR was substantially elevated (CA125 $\geq$ 35 U/ml and CD4/CD8 $\geq$ 1.8, score 2, HR = 2.76, 95% confidence interval: 2.04 to 3.74, $p < 0.001$).

Conclusions: A new scoring system based on the combination of the CA125 level with the CD4/CD8 ratio could further predict the prognosis of patients with advanced pancreatic cancer.

Keywords: Scoring system; Pancreatic ductal adenocarcinoma (PDAC); Peripheral lymphocyte subsets; CD4/CD8 ratio; CA125; Prognosis

Introduction

Pancreatic adenocarcinoma is the fourth leading cause of cancer-associated death in the United States and Europe.[1] Due to its extremely poor prognosis, pancreatic cancer is expected to become the second leading cause of cancer-related deaths in the USA by the year 2020.[2] Lacking early specific symptoms, patients are usually diagnosed at an advanced stage when surgical procedures are not available, and chemotherapy is their only option. Although these patients are usually classified as stage III or IV according to the 7th edition of the American Joint Committee on Cancer (Chicago, IL, USA) and did not have a long life expectancy,

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http://dx.doi.org/10.1016/j.ejso.2017.07.010

Please cite this article in press as: Yang C, et al., The metastasis status and tumor burden-associated CA125 level combined with the CD4/CD8 ratio predicts the prognosis of patients with advanced pancreatic cancer: A new scoring system, Eur J Surg Oncol (2017), http://dx.doi.org/10.1016/j.ejso.2017.07.010

we found significant differences among their prognosis. The prognosis of advanced patients is extremely poor. Thus, a robust predictive system should be identified.

The development and progression of cancer highly depends on the status of the host's immune system.[3] T-helper cells (Th cells) and cytotoxic T cells (Tc cells, CTLs, T-killer cells, killer T cells), also known as CD4+ T cells and CD8+ T cells, form large proportions of the cells involved in cell-mediated immunology. Typically, the alteration of CD4+ T cells and CD8+ T cells in terms of either number or function will affect the immune conditions. Additionally, the immune status can predict the outcome of cancer. Previous studies have described the relationship between cellular immunity and cancer,[4,5] and maintaining the balance between CD4+ and CD8+ T cells is critical for tumor immunity. The CD4/CD8 ratio is correlated with prognosis in several cancers[6,7]; however, few studies have reported its function in pancreatic cancer. Tumor tissues from patients with advanced pancreatic cancer are difficult to obtain without surgical treatment. Additionally, few tissues can be obtained through fine-needle aspiration (FNA); therefore, we found it difficult to detect the local immunity status. Therefore, because peripheral blood is easily acquired for testing immune cells, we chose to study systemic peripheral blood immune cells rather than the local immune status.

Carbohydrate antigen 125 (CA125) was initially and commonly used in patients with epithelial ovarian cancer, and recent studies have discovered an important role of CA125 in pancreatic cancer. Although the level of CA19-9 is typically higher in most pancreatic cancer patients, the level of CA125 is often thought to indicate a high tumor burden and metastasis.[8] Pancreatic cancer patients with a high concentration of CA125 are likely to be at an advanced stage and are not recommended to undergo surgical treatment. A previous study also indicated that the treatment effect and development of disease can be measured through changes in CA125.

In the present study, a large retrospective cohort was examined to determine whether the combination of the CD4/CD8 ratio with the CA125 level is associated with survival in patients with advanced pancreatic cancer.

Methods

Design and patients

A retrospective cohort study consisting of 437 patients diagnosed with advanced pancreatic cancer from July 2010 to April 2016 was conducted. All patients received their primary medical care at Shanghai Cancer Center, Fudan University. The patients who met the following criteria were eligible to participate in our study: 1) The participants were histologically or cytologically confirmed to have pancreatic adenocarcinoma and were not recommended for surgical treatment. The tumors were staged according to the 7th edition of the American Joint Committee on Cancer (Chicago, IL, USA) classification,[9] and patients with stage III and IV tumors were included. The diagnosis was made by two or more independent experienced attending physicians. Chemotherapy was the main treatment for the participants. 2) The patients were eligible to tolerate the adverse effects of chemotherapy at the primary time of treatment. If jaundice was found, bile drainage was performed prior to chemotherapy. 3) Sufficient liver function and renal function as well as a platelet counts within the normal range were also used as criteria. 4) Initial chemotherapy was performed at Shanghai Cancer Center, Fudan University. 5) No other primary malignant tumor was found during treatment. 6) The patients had no signs of immune system disease or a history of infection by bacteria or virus two weeks before major treatment. 7) The patients did not have any hematologic disorders.

The exclusion criteria included early-stage disease (stages I and II), a poor physical status, a tumor not originating from the pancreas, the lack of a surgical procedure, the absence of a pathological report, the absence of adequate laboratory information, jaundice, and active infection.

The primary end point was overall survival (OS), which was calculated from the date of diagnosis to the date of death or last follow-up. The secondary end point was progression-free survival (PFS), which was defined as the time from the date of diagnosis to the date of progression or death. An independent research assistant performed the follow-up assessment by telephone. Follow-up was performed every two months, and the last follow-up date was May 1, 2017.

All laboratory and imaging data were collected from the Electronic Medical Record System of Shanghai Cancer Center, Fudan University. The laboratory data were obtained at least three days prior to the initiation of major therapy.

All patients were provided information of the study, and informed consent was obtained from Shanghai Cancer Center, Fudan University. The study was approved by the Ethics Boards of the Shanghai Cancer Center.

Blood sample and flow cytometry

Before the decision regarding whether major therapy should be performed was made, peripheral blood samples were collected in heparinized tubes and immediately processed by flow cytometry as previously described.[10] Anti-CD4 (eBioscience) and anti-CD8 (eBioscience) antibodies were used, and the results are presented as the proportions of CD3+CD4+ and CD3+CD8+ cells in the total lymphocyte population. The CD4/CD8 ratio was defined as the proportion of CD4+ T cells divided by the proportion of CD8+ T cells. An electrochemiluminescence immunoassay was performed to measure the CA125 level using a Roche Cobas e601 (Roche MODU D + P model, D2400-P800)

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