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Tissue factor predicts response to chemotherapy in esophageal cancer

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ABSTRACT

Background: Neoadjuvant chemotherapy (NACT) improves the prognosis of patients with esophageal cancer who respond, but it is not effective in nonresponders. Therefore, it is crucial to establish a reliable method of predicting response before initiation of chemotherapy. Hypercoagulability, which is thought to be because of upregulation of tissue factor (TF) in cancer cells, was reported to be associated with chemoresistance. The aim of this study was to investigate the association between TF expression and response to NACT in esophageal cancer.

Methods: In 67 patients with advanced esophageal cancer, TF expression in pretreatment biopsy samples was evaluated immunohistochemically and correlated with clinicopathologic factors and response to chemotherapy.

Results: TF was expressed by 43.3% of the tumors, but there were no correlations observed with any clinicopathologic parameters examined. Clinical and histologic responses to chemotherapy were significantly worse in TF-positive patients compared with TF-negative patients. Multivariate analysis revealed that TF expression was significantly associated with a poor clinical response ($P = 0.0431$). TF expression was also independently associated with poor progression-free survival ($P = 0.0353$).

Conclusions: TF expression levels in pretreatment biopsy samples are useful for predicting response to NACT in advanced esophageal cancer. Further studies of mechanisms underlying the relationship between TF expression and chemosensitivity are needed.

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1. Introduction

Despite recent advances in surgical technique and perioperative management, surgery alone does not satisfactorily improve the prognosis of advanced esophageal cancer. Even after curative esophagectomy with extended three-field lymphadenectomy, cancer recurs in approximately 50% of patients [1]. Thus, it is highly likely that systemic micrometastases are present outside the surgical field at diagnosis. To improve the prognosis of advanced esophageal cancer, neoadjuvant chemotherapy (NACT), which is expected to eradicate systemic micrometastases, followed by surgery is a promising treatment strategy. Several recent studies have reported successful results with NACT [2,3]. Although NACT has been shown to improve the prognosis of patients that experience greater than a 50% decrease in the size of the primary tumor assessed by radiologic imaging, patients with less than a 50% decrease not only suffer from its side effects but also lose precious time to take advantage of alternative treatment options [2,4,5]. In some reports, the prognosis of nonresponders might be worse than those treated with a primary surgical approach [2,4,5]. Despite intensive efforts to identify predictors of response before initiating chemotherapy, there are currently no clear candidate predictors that can be used in daily clinical practice. Therefore, a reliable method that predicts response to chemotherapy is considered to be crucial for using NACT to treat advanced esophageal cancer going forward.

Activation of coagulation pathways frequently occurs in patients with cancer. Such hypercoagulopathy is considered the result of upregulation of tissue factor (TF) in cancer cells, which binds to coagulation factor VII (FVII) and its active form (FVIIa), thus initiating the coagulation cascade *via* the extrinsic pathway. In addition to its role in coagulation, accumulating evidence suggests that TF regulates intracellular signaling pathways that play a crucial role in inflammation, angiogenesis, tumor development, and metastasis [6–8]. Indeed, a high expression of TF is correlated with tumor grade, metastasis, and poor prognosis in various types of cancers [9–11]. In addition, a hypercoagulable state has been reported to be associated with chemoresistance [12]. In esophageal cancer, we previously reported that pretreatment plasma D-dimer levels, a marker of hypercoagulopathy, can be used as a predictor of chemosensitivity [13]. However, there have been few studies analyzing the correlation between TF and chemosensitivity. The present study investigates the association between TF expression levels in pretreatment biopsy samples and response to NACT in patients with advanced esophageal cancer.

2. Materials and methods

2.1. Patients

Between January 2004 and December 2010, a total of 288 patients with squamous cell carcinoma of the thoracic esophagus underwent esophagectomy at our hospital. Of these 288 patients, 176 patients underwent surgery without neoadjuvant treatment, 87 patients underwent NACT (FAP therapy (5-fluorouracil [5-FU] + Doxorubicin hydrochroride + cisplatin [CDDP]), $n = 78$; 5-FU + CDDP, $n = 9$) followed by surgery, and 25 patients underwent neoadjuvant chemoradiotherapy followed by surgery. Of the 78 patients who underwent neoadjuvant FAP therapy, we were able to collect biopsy samples containing tumor cells from 67 patients. All patients underwent esophagoscopy and computed tomography (CT) from the neck to the abdomen for tumor staging based on the seventh edition of the Union for International Cancer Control Tumour, Node, Metastases classification system [14].

2.2. Treatment protocol and follow-up

The FAP regimen consisted of CDDP at a dose of 70 mg/m^2 and Adriamycin at a dose of 35 mg/m^2 by drip infusion on day 1. On days 1 through 7, 5-FU was administered at a dose of 700 mg/m^2 daily by continuous infusion. Two cycles of chemotherapy were given, separated by a 3-wk interval [15–17]. Patients were scheduled for surgery approximately 4 wk after the last day of chemotherapy. Surgical therapy consisted of *en bloc* esophagectomy *via* right thoracotomy with two- or three-field lymphadenectomy and reconstruction using the stomach, jejunum, or colon. After surgery, patients were surveyed every 3 mo by physical examination and measurement of serum tumor markers (squamous cell carcinoma antigen and carcinoembryonic antigen), every 6 mo by CT and abdominal ultrasonography, and annually by endoscopy until tumor recurrence was evident.

2.3. Evaluation of the response to chemotherapy

The effect of chemotherapy was evaluated using two different methods. The clinical response to chemotherapy was evaluated based on the difference in tumor size between the CT scan 2 wk after completion of chemotherapy and the scan before chemotherapy. The largest area of the primary tumor was measured in two dimensions, the greatest diameter and the greatest perpendicular distance. The reduction rate was calculated as follows: (tumor area before treatment − tumor area after treatment)/(tumor area before treatment). Patients with more than a 50% decrease in the size of the primary tumor after NACT were defined as responders. The histologic response to chemotherapy was evaluated by the proportion of viable cancer cells in the entire tumor, based on hematoxylin and eosin–stained sections of surgical specimens. Criteria established by the Japanese Society for Esophageal Diseases [18]: grade 0, no histologic effect; grade 1, viable cancer cells accounted for more than one-third of the tumor tissue; grade 2, viable cancer cells account for less than one-third of the tumor tissue; and grade 3, no residual viable cancer cells.

2.4. Immunohistochemical staining

Biopsy samples were fixed in 10% formalin and embedded in paraffin using conventional techniques. Serial sections were prepared for hematoxylin and eosin staining to confirm the presence of tumor cells and to perform TF immunohistochemical studies. Immunohistochemistry was conducted as follows: after deparaffinization in xylene and dehydration in