Int J Clin Exp Med 2016;9(5):8536-8542
www.ijcem.com /ISSN:1940-5901/IJCEM0016056

*Original Article*

# Clinical significance of serum thymidine kinase 1 (TK1) expression in patients with non-small cell lung cancer

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Received September 12, 2015; Accepted March 28, 2016; Epub May 15, 2016; Published May 30, 2016

**Abstract:** Thymidine kinase 1 (TK1) is an enzyme involved in nucleic acid synthesis and is therefore considered to be an important marker of tumor proliferation. In this study, the use of serum thymidine kinase 1 expression for the diagnosis, treatment, and prognosis of patients with non-small cell lung cancer (NSCLC) following chemotherapy was investigated. The TK1 values of NSCLC patients were determined by a high-sensitivity enhanced chemiluminescence (ECL) dot blot assay. Through self-control prospectively observation TK1 levels before and after chemotherapy of 60 NSCLC patients, and through analyzing the relationship between the value of TK1 with NSCLC patients and clinical, pathological parameters, the efficacy of chemotherapy, in which are 32 male cases (53%) and 28 female cases (47%). Patients were in the age range of 35-79 years and the average age was 62 years. The pathological types included squamous cell carcinoma in 21 patients (35.3%), adenocarcinoma in 39 patients (64.7%). Pathological grade I was confirmed in 4 patients (5.9%), grade II in 21 patients (35.3%), and grade III in 35 patients (58.8%). It was also found that 7 patients (11.8%), 7 patients (11.8%), 14 patients (23.5%), and 32 patients (52.9%) were at clinical stage I, II, III, and IV, respectively. The study revealed that TK1 expression was positively correlated with NSCLC TNM staging. TK1 expression was positively related to the extent of NSCLC cell differentiation, namely, grade III>II>I; TK1 expression was negatively correlated with the efficacy of NSCLC chemotherapy. In conclusion, TK1 can monitor the efficacy of treatment in NSCLC patients and thus provide a reference value for chemotherapy as well as the prognostics markers.

**Keywords:** Serum cytoplasmicthymidine kinase 1, non-small cell lung cancer, chemotherapy, efficacy, prognosis

## Introduction

Lung cancer is the most common malignancy in the world, and compared to all other tumors, its incidence and cancer-related mortality are the highest [1]. Currently, there are no biomarkers that can be used for early detection and to monitor lung cancer [2]. The only recommended detection tool for early diagnosis of lung cancer is low-dose computed tomographic (CT) scanning. The US National Lung Screening Trial reported 20% reduced mortality for high-risk individuals screened with spiral CT scans [3]. Despite its promising potential, there are many disadvantages of this screening method, including cost, radiation exposure, and unequal adoption among insurance carriers. The possibility of developing a serum test for early lung cancer detection is attractive due to the ease of obtaining reference samples, as well as the minimal risk involved. There have been many attempts to detect specific proteins or genetic material in the serum or sputum of lung cancer patients, but these have all failed due to the lack of detection sensitivity for small amounts of material from patients at the early-stage of the disease.

Thymidine kinase 1 (TK1) is a well-established cancer biomarker that is elevated in the patient serum and tumor tissue of many hematological and solid tumor types, including lung cancer [4-6]. TK1 is efficacious as both a diagnostic and prognostic tool, since changes in serum TK1 levels reflect a patient's response to treatment and risk for recurrence [7-9]. TK1 is elevated in the very early stages of malignancy.

So far, no large clinical trials have been reported on TK1 expression in the serum of patients

**Table 1.** The associations between TK1 levels and clinicopathological features of the NSCLC patients

| Groups | The expression of TK1 | | $\chi^2$ | P |
|---|---|---|---|---|
| | Positive | Negative | | |
| Gender | | | 0.23 | > 0.05 |
| Male | 14 | 18 | | |
| Female | 21 | 7 | | |
| Pathological type | | | 0.17 | > 0.05 |
| Adenocarcinoma | 21 | 18 | | |
| Squamous cell carcinoma | 14 | 7 | | |

**Table 2.** The relationship between the TK1 level and the pathological grade and clinical stage ($\bar{x}\pm s$)

| Groups | N | TK1 (pm/L) |
|---|---|---|
| Pathological grade | | |
| Grade I | 4 | 1.53±0.53 |
| Grade II | 21 | 3.40±2.35* |
| Grade III | 35 | 3.58±2.51* |
| Clinical stage | | |
| Stage I | 7 | 1.51±0.52 |
| Stage II | 7 | 2.18±2.94* |
| Stage III | 14 | 2.55±1.70* |
| Stage IV | 32 | 4.35±5.23* |

Note: *Indicates that this group compared with above every groups $P < 0.01$.

with non-small cell lung cancer (NSCLC) following chemotherapy, evaluating treatment and prognosis. Serum TK1 levels have previously been correlated with baseline clinical and laboratory parameters and overall outcome.

In this study, we used an enhanced chemiluminescent (ECL) [10] dot-blot detection system to determine TK1 levels before and after chemotherapy in NSCLC patients; the efficacy of chemotherapy was determined by analyzing the relationship between the value of TK1 and the clinical as well as pathological parameters. The results show that TK1 can monitor the effectiveness of the treatment, and thus provide a reference value for chemotherapy as well as serve as a prognostic marker.

## Methods

*Patients*

A prospective, self-control study was performed on 60 NSCLC patients who were inpatients at the Department of Oncology in the First Affiliated Hospital of Bengbu Medical College from July 2011 to December 2012. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the First Affiliated Hospital of Bengbu Medical College. Written informed consent was obtained from all participants.

All lung tumors were confirmed by biopsy, bronchoscopy biopsy, or pleural fluid cytology diagnosis of NSCLC. Complete CT and laboratory examinations were obtained. All patients were assessed by the same medical oncologist from whom they received chemotherapy. Patient characteristics were as follows: gender: 32 male patients (53%), 28 female patients (47%); age: between 35 and 79 years, with an average of 62 years. According to the WHO histological classification and grading standards for lung cancer in 2004, 21 patients had squamous cell carcinoma (35.3%), and 39 patients had adenocarcinoma (64.7%). Pathological grading: 4 patients with Grade I (5.9%), 21 patients with grade II (35.3%), and 35 patients with grade III (58.8%). Tumor, Lymph nodes, Metastasis (TNM) staging: 7 patients with stage I (11.8%), 7 patients with stage II (11.8%), 14 patients with stage III (23.5%), and 32 patients with stage IV (52.9%). [TNM staging was performed according to the American Joint Committee on Cancer (AJCC) staging system's TNM staging classification].

*Treatment*

Patients within stage I or II were refused surgery, or had contraindications to surgery. All patients were checked for serum TK1 and underwent enhanced chest CT before and after chemotherapy, with 2 cycles of first-line platinum-containing two-drug regimen (the regimen was administered as follow for 3 to 4 weeks: Cisplatin 50-60 mg/m$^2$ or Carboplatin AUC 4-5, infusion, d1; Paclitaxel 135-175 mg/m$^2$ infusion 3-4 h, d1; or Vinorelbine 25 mg/m$^2$ infusion 6-10 min, d1, 8; or Gemcitabine 1000 mg/m$^2$ infusion 30 min, d1, 8). And review the chest CT evaluation recent efficacy. Effective evaluation was performed using WHO RECIST criteria.

*Treatment responses*

Complete response (CR) means the tumor disappeared. Partial response (PR) means the

**Table 3.** The relationship between the TK1 level and chemotherapy efficacy

| Groups | CT Imaging efficacy | | $\chi^2$ | *P* value |
|---|---|---|---|---|
| | Positive | Negative | | |
| TK1 difference | | | 8.07 | < 0.005 |
| Positive | 11 | 13 | | |
| Negative | 2 | 34 | | |

tumor partially disappeared, and the reduction in tumor size was 30% or greater. Stable disease (SD) means the tumor size showed no obvious changes. Progressive disease (PD) means the deterioration of the tumor.

*Specimen collection and detection*

2 ml of venous blood was collected from each of the NSCLC patients before and after treatment. The blood was collected with a drying tube, without anticoagulant. Permitting natural clotting, blood was sent for TK1 detection. The expression of TK1 was measured using an enhanced chemiluminescence (ECL) dot-blot assay, according to the manufacturer's instructions (Thymidine Kinase 1 Diagnostic Kit, SSTK Ltd., Shenzhen, China).

*TK1 assay*

Serum samples were collected 1 day before chemotherapy, and on day 1 and day 28 after the start of chemotherapy. The ECL dot-blot assay was performed according to the manufacturer's protocol. Blood sample of 2 ml was collected in the morning between 7 and 9 a.m. from subjects fasted for who did not take any breakfast. The drawn venous blood in non-heparin tube was stored for 2-3 h at room temperature (RT), centrifuged at 4,000 rpm for 10 min, and then stored at -20°C before analysis. Three microliters of serum was directly applied onto an Amersham Hybond ECL membrane (GE Healthcare, UK). The concentrations of purified TK1 (20, 6.6, and 2.2 pM) were used as positive extrapolation standards. The membrane was blocked in a Tris-buffered saline (TBS) solution with 6% non-fat milk for 1 h, and then primary anti-TK1 antibody was added and incubation continued at room temperature (RT) for 2 h. After incubation with a biotinylated secondary antibody for 40 min at RT, the membrane was incubated in a TBS solution with avidin/streptavidin-HRP; followed by addition of the ECL substrate. The light intensity of the spots on the membrane was detected by a CIS-1 imaging system (SSTK Ltd., Shenzhen, China). From the light intensities of the TK1 standard of known concentrations, the light intensities of the serum TK1 spots were re-calculated and expressed as pM. The sensitivity of the assay was < 0.3 pM, and the coefficient of variation value of duplicates was 5%. All tests were done blinded, and in duplicate.

*Results to determine*

Elevated serum TK1 was defined as an expression > 2.0 pM. Any serum TK1 value > 2 pM/L was regarded as positive.

*Statistical methods*

For the effect of chemotherapy, as determined by CT imaging, a positive definition for a curative effect was ascribed to events of CR, PR, SD, and a negative definition was ascribed to events of PD. All data was processed using the SPSS 17.0 statistical package (SPSS Inc., USA). Test data were expressed as mean ± s. Pairwise groups of data were compared with a Student's *t*-test. The positive rate was compared with a $\chi^2$-test. $P < 0.05$ was considered statistically significant.

## Results

*Clinicopathological features with serum TK1*

The value of TK1 was not significantly different in males vs. females, or in Adenocarcinomas vs. Squamous cell carcinomas (**Table 1**).

*Serum TK1 with pathological grade and clinical stage*

The expression of TK1 was positively correlated with the degree of cell differentiation in NSCLC: Grade III > grade II > grade I (**Table 2**). The expression of TK1 was positively correlated with the TNM staging in NSCLC (**Table 2**).

*The relationship between the TK1 level and chemotherapy efficacy*

As the difference of TK1 between after and before chemotherapy was < 0 (i.e. a radiographic efficacy of PD), TK1 level was negatively related with chemotherapy efficacy (**Table 3**).

*The relationship between the TK1 level and chest CT efficacy*

In a case of non-small cell lung cancer before and after chemotherapy in patients with chest

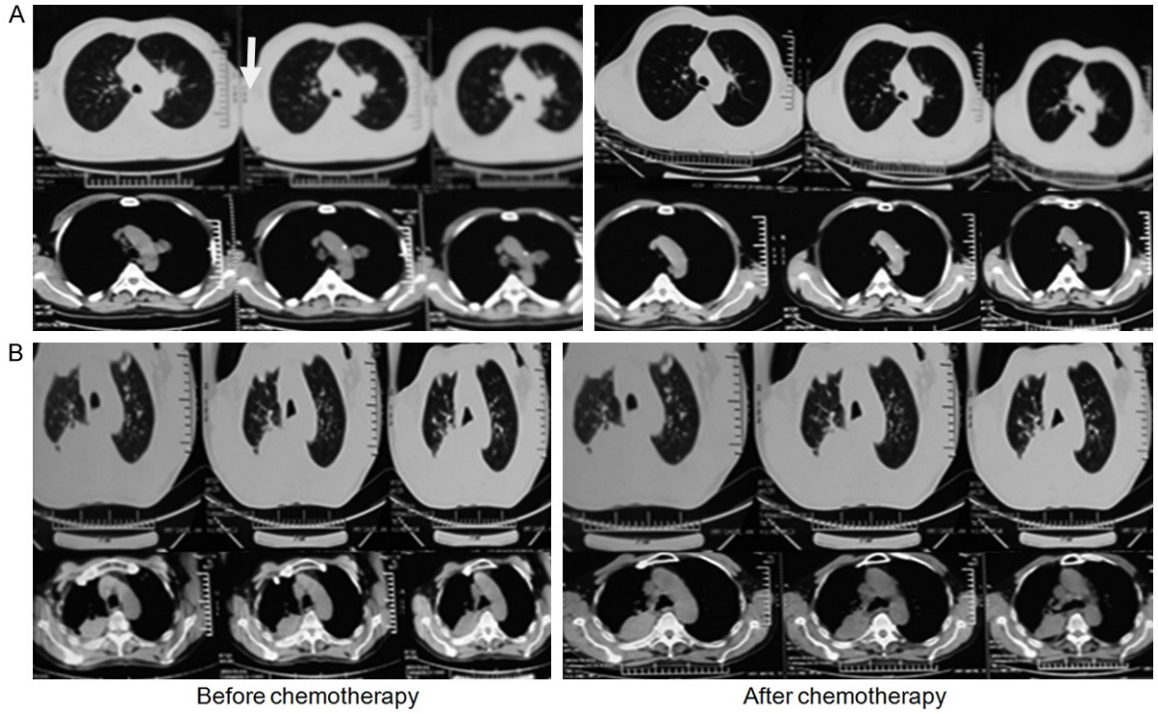


**Figure 1.** Two cases of non-small cell lung cancer before and after chemotherapy in patients with chest CT images. A: Typical Case 1: After chemotherapy, CT image changes show left lung tumor after chemotherapy significantly narrowed (response: PR); B: Typical Case 2: After chemotherapy, CT image changes mean right lung tumor increased (response: PD).

CT image change, a left lung tumor significantly narrowed (i.e. response: PR); concurrently, the blood serum TK1 value dropped significantly (**Figure 1A**). In another case of non-small cell lung cancer before and after chemotherapy in patients with chest CT image change, a right lung tumor after chemotherapy increased (i.e. response: PD); concurrent with that, the blood serum TK1 value increased (**Figure 1B**).

## Discussion

Cancer development and progression are complex biological processes; the actual causes and the exact mechanisms are still unknown. However, dysfunction in the regulation of cell proliferation and the cell cycle are known to be a fundamental event in any malignant transformation.

Thymidine kinase 1 (TK1) is a very significant regulator of the mammalian cell cycle and cell proliferation. TK1 is one of the key enzymes in the cell before DNA synthesis. As an important regulator of entry into the cell cycle, TK1 is primarily elevated during S phase [11, 12]. Normal cells showed a rise of TK enzyme activity near the G1/S boundary, and in G2 the levels return to approximately those at G1 [13].

The function and role of TK1 in neoplastic disease has therefore been extensively studied, primarily as a diagnostic biomarker for a variety of cancer types. As a biomarker, higher serum TK1 activity levels correlate with a more advanced cancer stage and grade [14-16]. Serum TK1 levels also show prognostic potential, as their levels help predict future relapse at the time of primary diagnosis in breast and colorectal cancer patients [9, 17].

As early diagnosis is key to effective cancer treatment, it is important to detect the upregulation of serum TK1. Alegre et al. showed that TK1 is upregulated in precancerous tissues, and remains elevated in correlation to cancer stage [18]. This confirmed earlier research that indicated that elevated TK1 levels correlated with early recurrence. TK1 appears to be upregulated as an early event in most tumors, and therefore can possibly be used in connection with other diagnostic and prognostic tech-

niques to improve patient outcome. These results also indicate that TK1-positive, yet pathologically normal, tumor margins may in fact be tumor cells that have escaped pathological identification. Our preliminary research indicates that TK1 can be used to identify possibly malignant cells that have evaded pathological detection during surgical removal.

Recently, serum TK1 has been most-widely tested in solid tumors, including gastric cancer, particularly for monitoring the effect of tumor therapies, prognosis, and follow-up [19]. The serum TK1 assay is commonly used to follow systemic chemotherapy in human and animals [19-24]. The effect of treatments that do not, in themselves, influence the TK1 value can be concluded from values obtained before and after a treatment cycle: if the TK1 level decreases, therapy can be concluded to be effective; while increasing TK1 levels indicate that the therapy is inefficient.

A study by Huang et al. showed that elevated thymidine kinase 1 in serum following neoadjuvant chemotherapy predicts poor outcome for patients with locally advanced breast cancer [20]. After a median follow-up of 30 months, the results indicated a statistically significant trend: patients with high serum TK1 expression had a significantly higher incidence of recurrence ($P = 0.006$), and cancer death ($P = 0.0128$), than those with low serum TK1 expression.

In non-small cell lung cancer (NSCLC), the significance of thymidine kinases for diagnostic, therapy monitoring, or prognostic purposes has been investigated by several authors in the last 20 years. In 1988, Yusa et al. investigated the increase of the cytosolic isozymes TK1 and TK2 in specimens of lung tumor patients, and the possible application of TK as a marker for malignant behavior and prognosis using gel electrophoresis. They showed that poorly differentiated tumors exhibited significantly higher activities of TK1 than moderately differentiated tumors [25].

Furthermore, this was also seen in the clinical course of the tumors with and without recurrence within 12 months after primary resection. In this study, TK1 in preoperative NSCLC patients, including non-metastatic and metastatic patients, was investigated. It was shown that the expression of TK1 in preoperative NSCLC patients was significantly higher than TK1 of healthy individuals ($P < 0.0001$). Moreover, a significantly higher preoperative TK1 expression was found in patients with T2 tumors as compared to T1 ($P = 0.042$), and in T3/T4 compared to T1/T2 ($P = 0.01$). The TK1 expression 1 month after surgery had significantly declined, compared to the expressions of TK1 preoperatively ($P < 0.001$) [25]. Apart from its prognostic value, TK1 was suggested as a reliable marker for monitoring the response to surgery in NSCLC patients [26].

Recently, Holdenrieder et al. published that preoperative serum TK1 (sTK1) levels show a high prognostic value for overall survival in NSCLC patients. A cut off of 20 U/l was selected, and the median survival time in patients with a sTK1 ≥ 20 U/l was only 3.1 months, whereas it was 9.0 months in patients with TK1 levels < 20 U/l [27]. A further study investigated the sTK1 of 157 NSCLC patients as a prognostic factor in routine clinical settings. sTK1 expression in patients with NSCLC was significantly higher than that of healthy controls ($P = 0.01$). Furthermore, the sTK1 value of NSCLC patients with squamous cell carcinoma was significantly higher as compared to those with adenocarcinoma ($P = 0.024$). A correlation of mean sTK1 levels to T-values ($P = 0.001$), stage ($P = 0.035$), and to size of the tumor ($P = 0.030$) was also shown. The sTK1 value and the number of sTK1 positive patients were also higher in NSCLC patients with disease recurrence [28].

Our study showed that serum TK1 expression was positively correlated with the degree of differentiation of NSCLC cells (that is, grade III > grade II > grade I); TK1 expression was positively correlated with the TNM staging of NSCLC, tumor increase, lymph node metastasis, and distant metastasis. The value of TK1 was not significantly different in male vs. female subjects, or in Adenocarcinomas vs. Squamous cell carcinomas. The latter result is inconsistent with Aufderklamm et al. [29], the reason for which is not clear. TK1 expression was negatively correlated with NSCLC chemotherapy efficacy. In a clinical chemotherapy cycle, increased TK1 levels indicating poor efficacy, and therefore disease progression, should call for a change in the chemotherapy regimen. The

high STK1 values in SD patients are probably due to residual tumor presence, or chemotherapy resistance. This indicates that these patients should be changed from the type of treatment, or received a changed dose of the cytostatic agents used. On the contrary, as decreased TK1 levels indicate good efficacy, and thus the original chemotherapy should be continued. If TK1 levels return to normal, a cessation of chemotherapy, or a shortened cycle of chemotherapy, should be considered.

Meanwhile, our study found serum TK1 expression in NSCLC patients was correlated with CT Imaging efficacy (**Figure 1A**). When TK1 value in patients with NSCLC declined, CT Imaging showed that tumor size shrunk. On the contrary, when TK1 values in patients with NSCLC increased, CT Imaging showed that tumor size increased (**Figure 1B**). This means that serum levels of tumor marker TK1 can be used in clinical settings as adjuvant or surrogate markers for estimation of tumor treatment response, particularly in patients with no measurable lesions. The TK1 assay is fast, sensitive, specificity, economical, and easily performed for measuring serum TK1 activity.

In summary, serum TK1 as a new marker of tumor cell proliferation applies for NSCLC patients. TK1 has diagnostic value in NSCLC, and has positive correlation with clinical stage, as measured by pathological grade cytology. It also can be a valuable reference for the guidance NSCLC patient chemotherapy, and evaluating the efficacy of chemotherapy, as a diagnostic advantage to CT. Therefore, serum TK1 may be served as an NSCLC marker in the future. Further work is needed to explore TK1 activity better in a longer period of follow-up, and a larger population of patients with solid tumor.

## Disclosure of conflict of interest

None.

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