# Serum Thymidine Kinase 1 Activity in the Prognosis and Monitoring of Chemotherapy in Lung Cancer Patients: A Brief Report

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**Introduction:** Thymidine kinase 1 (TK1) is a metabolic enzyme involved in DNA synthesis. Most standard treatment protocols for lung cancer (LC) include cytotoxic agents, which are potential modulators of TK1. We aimed to assess the prognostic significance of serum TK1 activity and its role in monitoring chemotherapy in LC patients.

**Methods:** TK1 activity was measured using the DiviTum (Biovica) assay in sera from 233 patients with non–small-cell lung cancer (NSCLC), 91 with small-cell lung cancer (SCLC), and 90 with benign lung disease.

**Results:** TK1 activity was significantly associated with age, performance status, and stage in NSCLC and with stage and weight loss in SCLC. In multivariate analysis, pretreatment TK1 activity, adjusted for performance status, stage, and weight loss, independently affected survival in NSCLC (relative risk =1.45, $p = 0.031$) and SCLC (relative risk = 2.49, $p = 0.001$). In NSCLC patients, adjusted elevated TK1 activity (>100 Du/L) at pretreatment was a significant predictor of treatment failure (odds ratio = 2.55, $p = 0.01$). A small (less than twofold) increase in TK1 activity after the first and second cycle of chemotherapy was significantly associated with treatment failure and poor overall survival.

**Conclusions:** Elevated pretreatment serum TK1 activity was an independent, adverse prognostic factor, based on survival, in the two main histological types of LC. A small (less than twofold) increase in TK1 activity after the first and second cycle of chemotherapy was associated with treatment failure and poor overall survival.

**Key Words:** Thymidine kinase 1, NSCLC, SCLC, Prognosis, Monitoring chemotherapy

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One of the most important biological mechanisms of cancer aggressiveness is related to uncontrolled tumor proliferation; its markers have been shown to have prognostic value when measured in lung cancer (LC) patients.[1,2] To take these measurements, however, a biopsy or resection may be required. One such marker is thymidine kinase 1 (TK1), which is the key cytosolic enzyme in the salvage pathway for deoxythymidine monophosphate (dTMP) synthesis; because TK1 is involved in DNA synthesis, it is considered a marker for cell proliferation. Notably, dividing cells release TK1 during mitotic exit, which is mediated by the ubiquitin system.[3] Thus, TK1 activity can be detected in the serum.

Recently, a new highly sensitive assay for the measurement of TK activity in serum has been developed that is based on immobilization of the phosphorylated reaction product by incorporation into DNA.[4] Korkmaz et al.[5] evaluated this assay in a small group of 48 patients with advanced non–small-cell lung cancer (NSCLC) and found a significant correlation between serum TK1 activity and primary tumor maximum standardized uptake, based on 18-fluorodeoxyglucose positron emission tomography scans, and overall survival. The present study was aimed to assess the prognostic significance of the new TK1 assay in the two main histological types of LC, NSCLC and small-cell lung cancer (SCLC).

Although TK1 levels detected in the serum primarily reflect proliferative activity, this enzyme is an important element of a complex system of kinases in the salvage pathway, complementing the main de novo pathway of dTMP synthesis. The activities of the two pathways are coordinated with the transport systems of nucleosides.[6] There are many factors modifying these systems. Most standard treatment protocols for LC include cytotoxic agents that are potential modulators of TK1 activity.[6–8] Therefore, we investigated the usefulness of this assay to monitor treatment with these agents.

## METHODS AND PATIENTS

This prospective study was performed on consecutive patients between November 1, 2008, and October 30, 2013. It was approved by the Institutional Ethical Review Board (0441-08-HMO) and included 90 patients with benign lung disease

**TABLE 1.** Distribution of TK1 Activity in Patients With Benign Lung Disease or Lung Cancer

| | | Serum TK1 activity (Du/L) | | | | |
|---|---|---|---|---|---|---|
| **Study group** | ***n*** | **Mean** | **Median** | **IQR** | **95th Percentile** | ***p* value[a]** |
| All LC vs. BLD | | | | | | $p$ <0.001 |
| BLD | 90 | 188 | 74 | 29–186 | 855 | |
| All LC | 324 | 819 | 155 | 59–479 | 3481 | |
| All non—small-cell lung carcinoma | 233 | 468 | 129 | 56–344 | 1,484 | |
| Age (yr) | | | | | | $p$ = 0.001 |
| ≤62 | 112 | 509 | 178 | 76–514 | 1,593 | |
| >62 | 121 | 424 | 101 | 36–241 | 1,307 | |
| Gender | | | | | | $p$ = 0.259 |
| Male | 151 | 578 | 148 | 60–397 | 1,705 | |
| Female | 82 | 266 | 111 | 42–303 | 1,135 | |
| Smoking habits | | | | | | $p$ = 0.561 |
| Nonsmoker | 70 | 929 | 131 | 54–410 | 2, 184 | |
| Smoker/ex-smoker | 163 | 332 | 129 | 58–289 | 1, 496 | |
| Histological type | | | | | | $p$ = 0.571 |
| Adenocarcinoma | 145 | 536 | 108 | 46–341 | 1,450 | |
| Squamous | 59 | 393 | 181 | 60–358 | 1,520 | |
| Other | 29 | 283 | 135 | 42–336 | 1,509 | |
| Performance status | | | | | | $p$ = 0.024 |
| 0–1 | 190 | 302 | 114 | 56–292 | 1,348 | |
| ≥2 | 43 | 1216 | 222 | 82–697 | 3,138 | |
| Weight loss (kg) | | | | | | $p$ = 0.469 |
| ≤5 | 94 | 518 | 115 | 58–325 | 1, 407 | |
| >5 | 139 | 400 | 150 | 55–373 | 2, 083 | |
| TNM stage | | | | | | $p <$ 0.001 |
| I–II | 39 | 153 | 82 | 31–152 | 1, 158 | |
| III | 66 | 234 | 116 | 57–224 | 1, 213 | |
| IV | 128 | 653 | 181 | 63–514 | 1, 711 | |
| All small-cell lung carcinoma | 91 | 1,717 | 325 | 85–1478 | 6,132 | |
| Age | | | | | | $p$ = 0.278 |
| ≤62 | 44 | 1, 986 | 423 | 102–1555 | 5, 947 | |
| >62 | 47 | 1, 465 | 195 | 64–1477 | 9, 795 | |
| Gender | | | | | | $p$ = 0.118 |
| Male | 66 | 2,148 | 398 | 95–2,273 | 10,086 | |
| Female | 25 | 577 | 115 | 76–697 | 4, 036 | |
| Performance status | | | | | | $p$ = 0.177 |
| 0–1 | 54 | 1, 276 | 181 | 60–1,127 | 6, 104 | |
| ≥2 | 37 | 2, 298 | 414 | 98–1,883 | 14,586 | |
| Weight loss (kg) | | | | | | $p$ = 0.013 |
| ≤5 | 56 | 1, 018 | 159 | 50–843 | 5, 629 | |
| >5 | 35 | 2, 828 | 467 | 126–3,090 | 19,195 | |
| Stage | | | | | | $p$ = 0.007 |
| Limited | 32 | 362 | 139 | 82–400 | 2, 160 | |
| Extensive | 59 | 2, 452 | 535 | 95–3,090 | 12,124 | |

IQR, interquartile range; TK1, thymidine kinase 1; BLD, benign lung disease; LC, lung cancer.
[a]*p* values derived from Kruskal-Wallis and Mann-Whitney tests.

(BLD), 233 patients with NSCLC, and 91 patients with SCLC. The diagnoses of all lung tumors were confirmed pathologically.

After informed consent was given, serum samples were obtained from all patients, before the start of treatment, and stored at –80°C until analysis. Serum TK1 activity was measured with a colorimetric enzyme-linked immunosorbent assay kit (DiviTum; Biovica International AB, Uppsala, Sweden), as described previously.[9] TK1 levels were expressed in DiviTum units/L (Du/L).

 