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The prognostic significance of pretreatment plasma levels of insulin-like growth factor (IGF)-1, IGF-2, and IGF binding protein-3 in patients with advanced non-small cell lung cancer

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Summary
Purpose: Insulin-like growth factor (IGF) system is related to cell proliferation and tumor growth. We tested whether pretreatment plasma levels of IGF-1, IGF-2, and IGF binding protein (IGFBP)-3 would predict the prognosis in patients with advanced non-small cell lung cancer (NSCLC).
Methods: Plasma levels of IGF-1, IGF-2, and IGFBP-3 were measured using enzyme-linked immunoassays from 77 patients with advanced NSCLC enrolled in a phase II study of irinotecan plus cisplatin chemotherapy.
Results: IGF-2 and IGFBP-3 levels were elevated in female patients, non-squamous cell carcinoma, and never smokers. In a univariate Cox proportional hazards model, higher levels of IGF-1, IGF-2, and IGFBP-3 were predictive of longer progression-free ($P = 0.001$, 0.006, and 0.007, respectively) and overall survival ($P = 0.025$, <0.0001, and 0.001, respectively). Multivariate analysis revealed that IGF-1 and IGFBP-3 are independent factors for progression-free survival ($P < 0.0001$ and $P = 0.001$, respectively). In addition, IGF-1, IGF-2, and IGFBP-3 are independently predictive for overall survival ($P = 0.004$, 0.001, and 0.043, respectively).
Conclusions: High plasma levels of IGF-1, IGF-2, and IGFBP-3 were associated with good prognosis in patients with advanced NSCLC. Further validation of these results is needed to determine the prognostic significance of IGF system in advanced NSCLC.

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1. Introduction

The insulin-like growth factor (IGF) family is composed of two peptide ligands (IGF-1 and IGF-2), two cell surface receptors (IGF-1R and IGF-2R), and at least six specific IGF binding proteins (IGFBP-1 to IGFBP-6) [1]. As potent mitogens, both IGF-1 and IGF-2 exert their action predominantly through interaction with IGF-1R, which activates the tyrosine kinase and initiates mitogen-activated protein kinase and phosphatidylinositol 3-kinase pathways that favor proliferation and cell survival. Therefore, aberrant stimulation of IGF signaling can contribute to the development and progression of malignant growth. There are abundant data showing that IGF-1R regulates cancer cell proliferation, survival, and metastasis [2].

Unlike most other growth factors, IGFs occur in large concentrations in the circulation and have systemic, hormonal, and local paracrine effects on cell behavior [3]. In the circulation, IGFs bind mainly to the main IGF binding protein, IGFBP-3. IGFBP-3 transports IGFs in circulation and directs it to target tissues, protects degradation of IGFs and prolongs their half-lives. IGFBP-3 competes with receptors for free IGF-1 and IGF-2, thereby controls biologic actions of IGFs. Independent from its capacity of binding with IGFs, IGFBP-3 has its own actions including regulation of cell growth and induction of apoptosis [4].

During the past decade, dysregulation of IGF system has been recognized as an important step in the development and progression of several common cancers. Early studies suggested that high circulating IGF-1 levels are associated with an increased risk of prostate [5], breast [6], colorectal [7], and lung [8] cancers, whereas high IGFBP-3 levels are associated with a decreased risk [9,10]. However, a recent systemic review and meta-regression analysis demonstrated that the patterns of association differed between smoking-related and non-smoking related cancers. Total IGF-1 levels are positively associated with the risk of non-smoking related cancers including prostate, colorectal, and premenopausal breast cancer, but not with lung cancer. Meanwhile, total IGFBP-3 levels are positively associated with the risk of premenopausal breast cancer and inversely associated with the risk of smoking-related cancer. When excluding a recruitment-bias study, lung cancer risk was inversely associated with total IGFBP-3 levels [11]. Taken together, these findings suggest that the IGF system has a pivotal role in tumor biology. However, many questions still remain regarding the role of IGF system in lung cancer. Although a lot of studies evaluated the association of circulating levels of IGF system with lung cancer risk over the last years, little is known about the prognostic role of IGF system in patients with advanced NSCLC. Therefore, we examined the association of pretreatment plasma levels of IGF-1, IGF-2, and IGFBP-3 with the clinical outcome of patients with advanced NSCLC enrolled in a phase II study of irinotecan plus cisplatin chemotherapy to determine their values as prognostic biomarkers in advanced NSCLC.

2. Methods

2.1. Study population and sample collection

Between September 2002 and June 2003, a total of 81 chemo-naïve patients with advanced NSCLC were enrolled in a phase II study of irinotecan and cisplatin chemotherapy. This study subjects were described in detail elsewhere [12]. Treatment consisted of irinotecan 80 mg/m^2 i.v. on days 1 and 8 and cisplatin 60 mg/m^2 i.v. on day 1 of 21-day cycle. Of total 81 patients, pretreatment plasma samples were obtained from 77 patients. The median age was 59 years (range 29—76 years). Sixty (78%) patients were male and 59 (76%) patients had adenocarcinoma, which was the most common histology. The majority of patients had stage IV disease (79%). Twenty-one healthy control subjects (11 males, 10 females) with median age of 59 (range 30—73) were also participated in this study. All patients gave written informed consent approved by the Institutional Review Board of the National Cancer Center Hospital. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Blood sample was drawn from each participant through venipuncture before chemotherapy and collected in a heparinized tube. The plasma was collected after centrifugation of the blood at 1500 rpm for 10 min at room temperature and was stored at −80 °C.

2.2. Measurements of plasma levels of IGF-1, IGF-2, and IGFBP-3

Commercially available immunoassay kits were used in the study to determine the plasma levels of IGF-1, IGF-2, and IGFBP-3 (Diagnostic Systems Laboratory, Webster, TX, USA) through enzyme-linked immunosorbent assay. The principle of the assays is based on quantitative sandwich enzyme immunoassay using precoated monoclonal antibody specific for human IGF-1, IGF-2, and IGFBP-3 onto a microplate for solid-phase ELISA. Briefly, 100 μL of plasma was used in each assay, and after following step-by-step protocol provided by the vendor, final absorbance of the developed color was determined using a microplate reader set to 450 nm with correction wavelength at 540 nm. IGF-1, IGF-2, and IGFBP-3 concentrations were extrapolated from the standard curves generated using recombinant human IGF-1, IGF-2, and IGFBP-3 in the assay.

Spearman correlation coefficients have been calculated between pairs of IGFs and IGFBP-3 in patients with advanced NSCLC. IGFBP-3 was strongly correlated with IGF-1 ($r = 0.514$, $P < 0.0001$) and IGF-2 ($r = 0.814$, $P < 0.0001$). IGF-1 was also correlated moderately with IGF-2 ($r = 0.355$, $P = 0.002$).

2.3. Statistical analysis

Associations between patients' clinicopathologic features and plasma levels of IGF-1, IGF-2, and IGFBP-3 were assessed by Mann—Whitney and Kruskal—Wallis tests for continuous