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MINI REVIEW

The role of IL-6 in immunotherapy of non-small cell lung cancer (NSCLC) with immune-related adverse events (irAEs)

Wanhai Ke[1], Li Zhang[2] & Yan Dai[1]

1 Arrhythmia Center, Fuwai Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China
2 Respiratory Medicine Department, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China

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Correspondence
Li Zhang, Respiratory Medicine Department, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing 100730, China.
Tel: +86 10 6915 5039
Fax: +86 10 6915 5039
Email: zhanglipumch@aliyun.com

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Abstract

IL-6 is a cytokine that plays an important role in response to injury or infection and is a promising biomarker for predicting poor prognosis and therapeutic targets in non-small cell lung cancer (NSCLC). This article reviews the biochemical mechanism, function and genotype of IL-6, and summarizes the diagnostic and prognostic value of IL-6 level. Anti-IL-6 therapy does not affect the effect of immunocheckpoint inhibitors (ICIs), but enhances its anticancer function, which may be the treatment option for immune-related adverse events (irAEs) in the future. Therefore, IL-6 may be a therapeutic target for the treatment of NSCLC.

Introduction

Immune checkpoint inhibitors bring immune-related adverse events

Lung cancer is the leading cause of cancer-related deaths worldwide, accounting for 18.4% of total cancer deaths.[1] Lung cancer can be divided into two main histological types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), of which NSCLC is the most common. Due to the low detection rate of early lung cancer and poor treatment effect of advanced lung cancer, the overall five-year survival rate of NSCLC is only 14%–17%.[2] Therefore, there is great interest in understanding the molecular and cytological processes of this invasive disease. In recent years, immunocheckpoint inhibitors (ICIs), especially the programmed cell death protein-1 (programmed death-1, PD-1) and their ligands, have changed the treatment model of NSCLC, significantly improving the response rate and durability of NSCLC.[3] ICIs play an important role mainly through cellular immune regulation.[4] As the core of fine cellular immune regulation, T cells play an irreplaceable role in the treatment of lung cancer. With the help of the MHC-I (major histocompatibility complex I), tumor cell antigen is presented to CD8 T cells, activating them to kill tumor cells, which not only depends on the antigen-specific signals mediated by T cell receptors, but also requires the participation of coordinated stimulus signal, mediated by some cytokines. T cell activation needs two coordinated stimulus signal, one of which is a CD80/86 combination of CD28 and the other is recognized by TCR cell antigen. However, the application of ICIs undermines the mechanism that should suppress the immune system and protect body tissues from the damage caused by the immune response, increasing the probability of TCR's self-antigen recognition and binding, thus increasing a series of immune related adverse events (irAEs). Many of these are driven by the same immune mechanisms that are responsible for the effect of drugs, or

that lead to irAEs. Biomarkers are urgently needed to identify, report and manage irAEs.

IL-6 as a biomarker to help predict and avoid irAEs

Cytokines refer to a variety of peptides and glycoproteins secreted by immunocompetent cells and tumor cells, including growth factors such as interleukin (IL), interferon (IFN), chemokines and tumor necrosis factor (TNF). IL-6 is one of these cytokines which play an important role in the response to injury or infection, participates in immune response, inflammation, hematopoiesis, and is even associated with the progression and apoptosis of a variety of tumors.[5] IL-6 will serve as a good biomarker to predict the poor outcome and therapeutic targets of NSCLC. In recent years, its role in NSCLC has attracted much attention. IL-6 may serve as a biomarker for irAEs to help predict, treat and even try to avoid irAEs.

Biochemical mechanism and function of IL-6

IL-6 binds to heterogeneous receptors containing ligands that bind the IL-6αchain (glycoprotein 80,GP80) and the common signal transduction subunit, gp130. IL-6 receptor (IL-6R) involvement leads to the activation of the tyrosine kinase Janus kinase (JAK) family, which in turn stimulates multiple pathways involved in MAPKs, phosphatidylinositol 3-kinase (PI3K), STATs, and other signaling proteins.[5] In approximately 50% of NSCLC derived cell lines,[6] signal transducer and activator of transcription 3 (STAT3) is continuously activated, and involved in almost all aspects of tumorigenesis, controlling cell cycle progression, tumor invasion and metastasis, host immune system evasion, and tumor angiogenesis[7] through complex mechanisms.

IL-6 genotypes and risk of lung cancer

The human IL6 gene is located on chromosome 7p21-24 and consists of five exons and four introns. The confirmed polymorphisms were −174 C/G (rs1800795)−6331 T/C (rs10499563) and −634 C/G (rs1800796). The relationship between IL6 polymorphisms and lung cancer risk is controversial. Several meta-analyses have concluded that IL6-174C/G polymorphism was not associated with lung cancer risk, while IL6-634C/G polymorphism may be associated with lung cancer susceptibility, suggesting that IL6-634c /G polymorphism is a smaller risk factor for lung cancer in the overall study population.[7] Further studies have shown that IL-6-634 polymorphism is associated with lung cancer risk in female non-smokers (OR = 2.45, 95% CI: 1.54–3.90). Moreover, both IL-6-634 CG or GG genotypes and a history of tuberculosis can increase the risk of lung cancer.[8]

Diagnostic and prognostic value of IL-6 level in NSCLC

Considering that tumor biomarkers are produced by tumor or nontumor cells in response to the presence of tumor cells, elevation of tumor biomarkers can be detected earlier than radiological abnormalities. To investigate IL-6 may serve as a specific molecular marker for NSCLC diagnosis. Islas-Vazquez *et al.*[9] recruited 28 patients with stage IV lung adenocarcinoma and found a significant increase in IL-6 level in the lung cancer group. In addition, elevated serum IL-6 levels were associated with lung cancer risk.[10]

IL-6 expression is associated with poor prognosis in lung cancer patient.[11] Elevated IL-6 level, severe malnutrition, and hypoalbuminemia were independent predictors of survival in advanced NSCLC patients.[12] Serum IL-6 levels (≥4.0 pg/mL) were associated with a significant reduction in lung cancer survival in African Americans and Caucasians.[13] Meta-analysis of nine studies involving a total of 1291 patients showed a significant correlation between high serum IL-6 concentration and poor prognosis in NCSLC patients.[14]

Direct evidence of effectiveness of IL6 as a biomarker of irAEs

During the course of ICI treatment, 10%–20% of patients receiving PD-1 inhibitors therapy developed unpredictable serious complications (irAEs). Unfortunately, although some baseline assessments have been noted,[15] no risk factors have been identified to predict irAEs. The preliminary experience with ICI treatment indicates that a significant number of patients present with clinical meeting criteria for systemic inflammatory response syndrome (SIRS), with characteristics similar to cytokine release syndrome (CRS).[16] These patients also developed other symptoms of irAEs, such as pneumonia, colitis, hepatitis, pancreatitis and endocrine diseases. Our initial experience with tocilizumab suggests that tocilizumab can be treated with SIRS-related symptoms, so do other irAEs.[16] C-reactive protein (CRP) is a downstream molecular product of IL-6 and thus it serves as a reliable surrogate marker for IL-6. Stroud *et al.* found that there was a statistically significant increase in CRP at the time of index irAEs.[17] As mentioned above, a significant proportion of irAEs patients have features similar to those of CRS. IL-6 level is known to rise during CRS.[18,19] Collectively, there is direct evidence of the effectiveness of IL6 as a biomarker of irAEs. With regard

to the above discussion and the diagnostic and prognostic value of IL-6 level in NSCLC, an assessment of baseline IL-6 level before ICI therapy followed by repeated measurements in case of irAE emergence could still be a useful biomarker.[20]

IL-6 levels can be used as a biomarker to assess the activity of irAEs and evaluate its role in treatment decisions, particularly in anti-IL-6 treatment. Meanwhile, it is feasible to obtain a baseline level of IL-6 in patients with lung cancer when taking advantage of ICI. To explore the correlation between IL-6 baseline level and the liability or severity of the irAEs, to explore the baseline level of IL-6 and the effect of ICI treatment is of great significance to guide the clinical decision-making of clinical medicine in irAEs patients and to predict the possibility of irAEs.[20] In other words, patients with different IL-6 baselines may have different treatment strategies.

Novel treatments associated with the mechanism of the IL-6

Tocilizumab targeted at cancer therapy and management of cancer related symptoms

Tocilizumab is a humanized monoclonal antibody with a high affinity for human IL-6 that has the potential to improve anemia, reduce cancer-related cachexia,[21] and improve significant symptom loads[22] such as pain, fatigue, distress, sleep disorders, etc, resulting in longer periods of time and more life-extending chemotherapy for patients. It has been reported that adding IL-6 to erlotinib-sensitive cells increased drug resistance compared to unadministered cells. Therefore, combination therapy with EGFR inhibitors and tocilizumab can reduce drug resistance in NSCLC patients.[23] Therefore, anti-IL-6 therapy is of great significant for tumor targeted therapy and the control of tumor-related symptoms.

Tocilizumab targeted at many irAE indications

At present, the first-line treatment strategy for irAEs is mainly immunosuppressive therapy, such as glucocorticoids and other immune modulators. But their use has raised concerns among users of ICIs because they are of the opinion that immunosuppressive therapy could affect the outcome of treatment. Glucocorticoids are drugs known to suppress the "priming" of immune responses. However, long-term use may impair ICI -mediated anti-tumor benefits. In addition, high doses and/or prolonged use of glucocorticoids can lead to severe systemic toxicity. Nevertheless, glucocorticoids remain the drugs of choice for the treatment of acute irAEs.

In recent years, anti-IL-6 therapy has become the choice of many indications for the treatment of acute irAEs, which not only does not affect the efficacy of ICI, but also enhances its anticancer function. Possible indications for anti-IL-6 treatment include severe irAEs in their acute phase, severe arthritis, uveitis, myocarditis, great vasculitis, Graves orbitopathy, severe pneumonia, myasthenia gravis, etc.[20,24–28] The 2009 NCCN guidelines[29] also recommend tocilizumab as an option for patients with severe musculoskeletal toxicity who do not show significant improvement after two weeks of glucocorticoids therapy. In a retrospective trial, Stroud *et al.*[17] found that in a group of patients with lung cancer who had already produced irAEs, serum IL-6 levels were significantly reduced after tocilizumab therapy. Of the 34 patients, 27 (79.4%) showed clinical improvement (defined as remission of symptoms or discharge within seven days), with 52.9% requiring only a single dose of tocilizumab. Therefore, Stroud *et al.* proposed tocilizumab as a second-line treatment for glucocorticoid resistance.[17]

Clinical evidence of tocilizumab when targeted at many irAE indications

At present, there is a paucity of clinical trial data on tocilizumab targeted at irAE indications with only scattered single center reports. Hopkins *et al.*[15] reported three melanoma patients who developed severe polyarthritis while receiving ICI therapy, and in which treatment with glucocorticoids resulted in poor efficacy or the recurrence of joint symptoms during the process of glucocorticoid reduction. They were then treated with tocilizumab, after which the symptoms significantly improved, and the dosage of glucocorticoids was reduced. Adverse events were not observed in all patients, and the therapeutic effect of ICI was not affected. All patients tolerated tocilizumab without adverse events.

Horisberger *et al.*[30] reported a case of stage IV lung adenocarcinoma who after receiving six months of treatment with nivolumab developed bilateral aseptic conjunctivitis, followed by oropharyngeal mucositis and esophagitis, and severe esophageal stenosis. Despite large doses of glucocorticoid therapy for the irAEs administered for several months, the patient experienced very rapid symptomatological reappearance during the glucocorticoid-reduction period, complicated by osteoporosis-induced fractures. As a result, tocilizumab (8 mg/kg) was administered and the symptoms and signs then began to improve significantly. During follow-up, the severe esophageal stenosis did not recur and the tumor did not progress.

Optimal dose and schedule of tocilizumab when targeted at many irAE indications

While tocilizumab is used as an indication for irAEs, the optimal dose and schedule of treatment for tocilizumab remains unclear. Considering economic factors and the patient's cancer status, Stroud *et al.*[17] recommended that patients taking glucocorticoids and sufficient to be admitted to the hospital because of irAEs, should be given tocilizumab intravenously at 4 mg/kg over one hour. For further cost savings, the dose of the drug may be less than 4 mg/kg, even if it is a single dose of 200 mg, which matches the dose of the current bottle (200 mg/10 mL). Another possible regimen reported by Martins *et al.* was 8 mg/kg of tocilizumab once a month, or 162 mg subcutaneously once a week.[20] However, this will be the subject of future research. The FDA has not yet approved drugs for irAEs refractory to glucocorticoid therapy and cost-minimization is of paramount importance.

Conclusion

This article systematically summarizes the molecular biological mechanism of IL-6, and proposes the diagnostic and predictive value of IL-6 for irAEs, as well as the advantages of anti-IL-6 treatment for irAEs in clinical cases for the first time. IL-6 is currently promising as a biomarker in predicting the prognosis of NSCLC and predicting irAE, but data from clinical trials are lacking. Tocilizumab has a unique advantage in the treatment of irAE without increasing the risk of tumor progression and without reducing the therapeutic effect of ICI,[31] and may become the first-line treatment for acute irAEs. However, there is currently a lack of standardized application of drug guidelines, which requires the support of clinical data and clinical trial guidelines.

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Disclosure

The authors report there are no conflicts of interest.

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