MINI REVIEW

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

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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. 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. In approximately 50% of NSCLC derived cell lines, 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 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)−633 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. 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.

**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. 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.

IL-6 expression is associated with poor prognosis in lung cancer patient. Elevated IL-6 level, severe malnutrition, and hypoalbuminemia were independent predictors of survival in advanced NSCLC patients. Serum IL-6 levels (≥4.0 pg/mL) were associated with a significant reduction in lung cancer survival in African Americans and Caucasians. 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.

**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, 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). 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. 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. 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. 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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{21} and improve significant symptom loads\textsuperscript{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.\textsuperscript{23} Therefore, anti-IL-6 therapy is of great significance 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 ICIIs 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 antitumor benefits. In addition, high doses and/or prolonged use of glucocorticoids can lead to severe systematic 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.\textsuperscript{20,24–28} The 2009 NCCN guidelines\textsuperscript{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 \textit{et al}.\textsuperscript{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 \textit{et al}. proposed tocilizumab as a second-line treatment for glucocorticoid resistance.\textsuperscript{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 \textit{et al}.\textsuperscript{15} 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 symptomological 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.\textsuperscript{11} 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.\textsuperscript{12} was 8 mg/kg of tocilizumab once a month, or 162 mg subcutaneously once a week.\textsuperscript{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,\textsuperscript{11} 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.

References

1 Bray F, Ferlay J, Soerjomataram I et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68 (6): 394–424.
2 Bodelon C, Polley MY, Kemp TJ et al. Circulating levels of immune and inflammatory markers and long versus short survival in early-stage lung cancer. Ann Oncol 2013; 24 (8): 2073–9.
3 Rafel H, El-Bahesh E, Finianos A et al. Immune-based therapies for non-small cell lung cancer. Anticancer Res 2017; 37 (2): 377–88.
4 Hradilova N, Sadilkova L, Palata O et al. Generation of dendritic cell-based vaccine using high hydrostatic pressure for non-small cell lung cancer immunotherapy. PLOS One 2017; 12 (2): e171539.
5 Hong DS, Angelo LS, Kurzrock R. Interleukin-6 and its receptor in cancer. Cancer 2007; 110 (9): 1911–28.
6 Haura EB. Activated epidermal growth factor receptor-stat-3 signaling promotes tumor survival in vivo in non-small cell lung cancer. Clin Cancer Res 2005; 11 (23): 8288–94.
7 Haura EB, Turkson J, Jove R. Mechanisms of disease: Insights into the emerging role of signal transducers and activators of transcription in cancer. Nat Clin Pract Oncol 2005; 2 (6): 315–24.
8 Su M, Zhou B. Association of genetic polymorphisms in IL-6 and IL-1beta gene with risk of lung cancer in female non-smokers. Zhongguo Fei Ai Za Zhi 2014; 17 (8): 612–7.
9 Islas-Vazquez L, Prado-Garcia H, Aguilar-Cazaures D et al. 529 LAP TGF-beta subset of CD4+CD25+CD127- Treg cells is increased and overexpresses LAP TGF-beta in lung adenocarcinoma patients. Eur J Cancer 2015; 51: S113.
10 Pine SR, Mechanic LE, Enewold L et al. Increased levels of circulating interleukin 6, interleukin 8, C-reactive protein, and risk of lung cancer. J Natl Cancer Inst 2011; 103 (14): 1112–22.
11 Brichory F M, Misek D E, Yim A M et al. An immune response manifested by the common occurrence of annexins I and II autoantibodies and high circulating levels of IL-6 in lung cancer. Proc Natl Acad Sci U S A 2001; 98 (17): 9824–9.
12 Ujije H, Tomida M, Akiyama H et al. Serum hepatocyte growth factor and interleukin-6 are effective prognostic markers for non-small cell lung cancer. Anticancer Res 2012; 32 (8): 3251–8.
13 Enewold L, Mechanic LE, Bowman ED et al. Serum concentrations of cytokines and lung cancer survival in African Americans and Caucasians. Cancer Epidemiol Biomarkers Prev 2009; 18 (1): 215–22.
14 Liao C, Yu Z, Guo W et al. Prognostic value of circulating inflammatory factors in non-small cell lung cancer: a systematic review and meta-analysis. Cancer Biomarkers 2014; 14 (6): 469–81.
15 Hopkins AM, Rowland A, Kichenadasse G et al. Predicting response and toxicity to immune checkpoint inhibitors using routinely available blood and clinical markers. Br J Cancer 2017; 117 (7): 913–20.
16 Sharma N, Stroud CRG, Walker PR. Systemic inflammatory response syndrome (SIRS) with immune checkpoint inhibitors. J Clin Oncol 2016; 34: 3061.
17 Stroud CR, Hegde A, Cherry C et al. Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade. J Oncol Pharm Pract 2018; 25 (3): 551–7.
18 Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: Recognition and management. Blood 2016; 127 (26): 3321–30.
19 Lee DW, Gardner R, Porter DL. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014; 124: 188–95.
20 Martins F, Sykiotis GP, Maillard M et al. New therapeutic perspectives to manage refractory immune checkpoint-related toxicities. Lancet Oncol 2019; 20 (1): e54–64.
21 Ando K, Takahashi F, Motojima S et al. Possible role for tocilizumab, an anti-interleukin-6 receptor antibody, in treating cancer cachexia. J Clin Oncol 2012; 31 (6): E69–72.
22 Laird BJA, Fallon M, Hjermstad MJ et al. Quality of life in patients with advanced cancer: Differential association with performance status and systemic inflammatory response. J Clin Oncol 2016; 34 (23): 2769–75.
23 Bayliss TJ, Smith JT, Schuster M, Dragney KH, Rigas JR. A humanized anti-IL-6 antibody (ALD518) in non-small cell lung cancer. Expert Opin Biol Ther 2011; 11 (12): 1663–8.
24 Dayer JM, Choy E. Therapeutic targets in rheumatoid arthritis: the interleukin-6 receptor. Rheumatology 2010; 49 (1): 15–24.
25 Hirano T, Ohguro N, Hohki S et al. A case of Behçet’s disease treated with a humanized anti-interleukin-6 receptor antibody, tocilizumab. Jpn J Rheumatol 2012; 22: 298–302.
26 Perdan-Pirkmajer K, Praprotnik S, Thomsic M. A case of refractory adult-onset Still’s disease successfully controlled with tocilizumab and a review of the literature. Clin Rheumatol 2010; 29 (12): 1465–7.
27 Muselier A, Bielefeld P, Bidot S, Vinit J, Besancenot JF, Bron A. Efficacy of tocilizumab in two patients with anti-TNF-alpha refractory uveitis. Ocul Immunol Inflamm 2011; 19 (5): 382–3.
28 Jonsson DI, Pirskanen R, Piehl F. Beneficial effect of tocilizumab in myasthenia gravis refractory to rituximab. Neuromuscul Disord 2017; 27: 565–8.
29 Thompson JA, Schneider B, Brahmer J et al. Management of immunotherapy-related toxicities, version 1.2019. J Natl Compr Canc Netw 2019; 17 (3): 255–89.
30 Horisberger A, La ROSAS, Zurcher J et al. A severe case of refractory esophageal stenosis induced by nivolumab and responding to tocilizumab therapy. J Immunother Cancer 2018; 6 (1): 156.
31 Davila ML, Riviere I, Wang X et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med 2014; 6 (224): 224r–5r.