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The Immune Regulatory Role of Cytokine-Induced Killer Cells Treatment on Non-Small Cell Lung Cancer Patients

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Abstract

Although a great progress has been made in surgery, radiotherapy and chemotherapy for non-small cell lung cancer (NSCLC), the 5-year overall survival rate (OS) remains unsatisfactory (approximately 15%). Recently, cytokine-induced killer (CIK) cells treatment as an adoptive immunotherapy has great promises in the scenario of potential new approaches for the treatment of lung tumors. Adaptive and innate cellular immunity are all important for inhibiting tumor growth and the clearance of cancer. The abilities to efficiently kill tumor cells and promote immune responses are the ultimate basic ability requested to CIK cells treatment. Therefore, we conducted a systematic review to evaluate the immunoregulation of CIK cells treatment in NSCLC patients to provide an objective reference for clinical decision-making.

Keywords: CIK, immune regulatory, NSCLC

1. Introduction

Lung cancer is a major cause of diagnosed cancer worldwide with a 5-year survival rate of less than 15% [1, 2]. Non-small cell lung cancer (NSCLC) accounts for about 80–85% of lung malignancies and shows high morbidity, high mortality and low survival rates. Most of these NSCLC patients are diagnosed at the late stage leading to a poor prognosis.

So far, the predominant applied cancer treatment methods are still surgery, radiation and chemotherapy; however, the effectiveness of these treatments is not completely satisfactory. These methods often have limited effects and often fail to completely remove minimal residual

cancer cells. Surgery is the predominant treatment method against for NSCLC; however, 60–70% of patients who receive surgery may eventually develop loco-regional recurrence or distant metastasis [3]. Chemotherapy may be useful, but drug resistance and adverse effects still remain; therefore, chemotherapy cannot be used for most of the patients due to the poor tolerance of the majority of later stage patients. Thus, the more effective and safer treatments are urgently needed [4], and tremendous efforts had been done to find new method that can offer better prospects to eradicate tumors.

Recently, adoptive immunotherapy is an evolving treatment approach based on the use of the immune system to treat cancer. Immunotherapy has become a hot area in cancer research and treatment in China. The rapid ex vivo generation of adoptive immune cells is a simpler, cheaper, and more efficient way to generate a potent immunotherapeutic product [5, 6]. Since the 1980s, there are different forms of adoptive immunotherapy used in clinical trials: lymphokine-activated killer cells (LAK), tumor-infiltrating lymphocytes cells (TIL), natural killer (NK), γ δ T-cells and cytokine-induced killer (CIK) cells, tumor-associated antigen (TAA)-specific cytotoxic T-cell (CTL), and other forms of cells have been extensively employed in adoptive immunotherapy [7].

Among them, CIK cells are a heterogeneous population of ex-vivo expanded T lymphocytes with diverse T-cell receptor (TCR) specificities and are endowed with nonmajor histocompatibility complex (MHC)-restricted activities against tumor cells. The antitumor activity is mainly, even if not exclusively, associated with the CD3⁺CD56⁺ cells [8]. The antitumor effects of CIK cells have been described against a number of hematologic and solid malignancies both in vitro and vivo. In vitro, CIK cells can kill tumor cells directly [9–11] and improve apoptosis of tumor cells [12], CIK cells also can reverse the drug resistance of A549/DDP [13], and other study found that CIK can alter the cytokine secretion profiles of some immune cells [14]. In vivo, CIK cells also showed significant antitumor activity in animal studies and clinical trials. In the severe combined immunodeficiency (SCID) mouse model, human CIK cells infusion significantly prolongs the survival of SCID mice when compared with control animals or animals infused with LAK cells [15]. In other studies, using the SCID model, CIK cells have in vivo antitumor activity against a number of hematopoietic and solid tumors [16]. Since 1991, CIK cells were reported by Schmidt-Wolf [15], and several clinical trials have been studied. The application of CIK cells as an adoptive immunotherapy is important for the treatment of cancer, since several clinical studies have confirmed the safety of CIK therapy for patients [17, 18]. Numerous clinical studies have been recently performed, whereby adjuvant infusions of CIK cells following surgical resection or chemotherapy demonstrated a significant increase in survival time [19, 20]. The first clinical study included 10 patients with metastatic renal carcinoma, colorectal cancer and lymphoma. One patient with lymphoma obtained a complete response while six patients had progressive diseases and three patients did not experience any change [21, 22]. Other clinical trials subsequently confirmed the safety and benefit of CIK cell-based therapy along with demonstration of initial clinical activity [23, 24]. But, in a recent review, it is reported that patients with localized NSCLC (stages I–III) using immunotherapy (excluding checkpoint inhibitors) did not get a survival benefit [25].

The host immune system plays a critical role in tumor surveillance and rejection. Innate and adaptive cellular immunity are all important for against tumor growth and the clearance of

cancer. Lung cancer is not typically regarded as an “immunogenic” malignancy, a growing body of evidence suggests that immune responses to lung tumors might be present, and their magnitude might correlate with patient outcome. According to previous studies, cancer patients have some dysfunctions in cellular immunity, including innate and adaptive immune responses [26]. Because of the low immune functions of lung cancer patients, effective immune response cannot be achieved. That is one of the reasons that malignant tumors are incurable [27, 28]. Autoimmune disorders in peripheral blood of lung cancer patients are demonstrated by lower levels of CD4⁺T, NK cells, DCs and higher levels of CD8⁺T cells [29–31]. Several studies showed that in peripheral blood, increased number of inhibitory cells such as regulatory T-cells (Tregs) and myeloid-derived suppressor cells (MDSCs) and inhibitory molecular such as PD-1 TIM-3 expressed on lymphocytes has been observed in patients with NSCLC, and other cancers [32–34]. Otherwise, in tumors tissue there are local immunological changes. Tumor-infiltrating lymphocytes (TILs) may play an important role in cell-mediated immunological destruction of tumors. Many studies demonstrated that there are more T-cells in tumors tissue in NSCLC compared with that in normal tissue [35, 36]. Accumulating evidence shows that levels of TILs are associated with improved recurrence-free survival in NSCLC patients as well as a reduced likelihood of systemic recurrence [37, 38]. A high density of tumor-infiltrating Tregs was reported to be associated with the recurrence of resected NSCLC [39].

The abilities to efficiently kill tumor cells and promote immune responses are the ultimate basic ability requested to adoptive immunotherapy. The number of immune cells particularly Th1 cells, CD8⁺ T-cells, and NK, NK T-cells is associated with the survival of cancer patients. Such antitumor cellular immune responses can be greatly enhanced by adoptive transfer of CIK cells [40, 41]. However, the immune regulation role of CIK cells treatment remains controversial. Therefore, in the present study, we conducted a review to evaluate the immunoregulation of CIK cells treatment in NSCLC patients, in order to provide an objective reference for clinical decision-making.

2. Immunoregulation of CIK cells treatment in NSCLC patients

2.1. The changes of lymphocytes of NSCLC patients in peripheral blood

According to previous studies, cancer patients exhibit certain dysfunctions in cellular immunity, including innate and adaptive immune responses [26]. Due to the low immune function displayed by patients with lung cancer, effective immune response cannot be achieved, and this is one of the reasons why malignant tumors are incurable [27, 28]. Autoimmune disorders in patients with lung cancer are demonstrated by reduced levels of CD4⁺ and CD3⁺CD56⁺ cells, and increased levels of CD8⁺ cells [29, 30]. The response of the human immune system against tumors mainly depends on cellular immunity [42]. CD3⁺ T-cells are mature T-cells, while CD4⁺ T-cells are considered to have a predefined role as Th cells [43]. It has been demonstrated that cytotoxicity against tumors is dependent on an appropriate interaction between CD4⁺ and CD8⁺ T-cells [44]. However, the ratios of T lymphocyte subsets in peripheral blood are usually disordered in cancer patients [45, 46]. The proportion of these cells in the human body must remain constant in order to maintain its optimal state of balance and participate

in cellular immune surveillance [47]. NK and NK T-cells are effector cells, which are involved in the immune response against tumors during the early stages of tumor development [48]. These cells do not require any specific antibodies or presensitized lymphocytes to exert their function and may be rapidly activated to suppress and destroy a variety of tumor cells [49]. In addition, NK and NK T-cells are more lethal upon being activated by lymphokines [49].

Many studies including our study found that the average percentage of CD3⁺CD4⁺, CD3⁺ and NK T-cells, as well as the levels of IFN- γ following several treatment courses, were significantly higher than the values observed prior to CIK cells treatment [50–52]. Of course, there are studies found that there are no changes after CIK cells treatment [25]. Here, we have to discuss about the course of CIK cells treatment. Fan et al. found that the median OS of the CIK cells treatment more than four cycles subgroup was significantly longer than that of less than four cycles subgroup [53]. Shi et al. [54] observed that the percentage of CD3⁺ and CD4⁺ cells, and the ratio of CD4⁺/CD8⁺ cells were significantly higher following the first course of CIK cells therapy, compared with the values prior to treatment. However, in our study, the percentages of CD3⁺ and CD3⁺CD4⁺ cells were observed to be no change following only one course of CIK cells therapy, which may be due to the difference in the detection time point (1 month in our study vs. 2 weeks in the study by Shi et al. subsequent to each course), and this result was consistent with others. Jin et al. [55] reported that only one treatment course of CIK cells treatment was unable to improve the immune function in patients with lung cancer. Several researches have reported that CD3⁺, CD3⁺CD4⁺ and other immune cells peaked at 4 weeks following CIK cells treatment, while circulating CIK cells persisted for ≤ 2 weeks following infusion [22]. Those studies suggested that several courses of CIK cells treatment would be required to achieve a stable effect [22, 55]. Therefore, to gain therapeutic efficacy, multiple courses of therapy should be administered to the patients.

Otherwise, the treatment done before CIK cells treatment may affect the immune status of NSCLS patients [50]. Thus, the treatments administered to the patients prior to CIK cells therapy seemed to affect the outcome, since more courses were required to achieve effective antitumor immune responses. At present, there is controversy regarding the number of cells required to be infused in CIK cells therapy, since the antitumor activity of CIK cells is mainly associated with the CD3⁺CD56⁺ fraction, rather than the CD8⁺ fraction, which constitutes the highest percentage of CIK cells [56]. A previous study suggested that the improvements in immune function exerted by CIK cells were affected by the number of CIK cells [22]. In our study, we found that the number of CD3⁺CD4⁺ and CD3⁺ T lymphocytes did not change following each course of CIK cells treatment. These demonstrated that the number of CIK cells did not affect lymphocyte-associated functions. By contrast, the number of NK and NK T-cells increased with the increase in the percentage of CD3⁺CD56⁺ cells, which enabled the patients to effectively kill tumor cells.

In most studies, patients received autologous CIK cells, allogeneic CIK cells may be applicable in the combination treatment in NSCLC [57, 58], median progression-free survival (mPFS) of allogeneic CIK cells treatment group was significantly longer than that of control group [57]. The study found that the levels of IL-2 and IFN- γ in serum did not differ significantly between the two groups both before and after the treatment. Moreover, there were

no obvious changes in the percentage of CD3⁺, CD3⁺CD4⁺, CD3⁺CD8⁺, CD4⁺/CD8⁺ T-cell ratio and NK cells before and after treatment. Wang et al. found that after allogeneic CIK cells treatment, the outcomes of immune function remained unchanged, but the median OS was higher in NSCLC patients receiving allogeneic CIK cells than control group [58]. The CIK cells used in clinical treatment are mostly induced by PBMC in the peripheral blood of patients with tumors. Autologous CIK cells may have the ability to recognize the surface markers of tumor cells and have strong anti-tumor activity. However, in recent years, it has been suggested that low immunity and poor activity of immune cell in patients with tumors may affect the efficacy of CIK cell therapy. Comparative studies of autologous and allogeneic CIK cells treatment have not been reported in lung cancer clinical study. One study had found that semi-allogeneic DC-CIK cells had a stronger anti-tumor effect than did autologous CIK cells in vitro [59]. The reason for this is that the immune function of cancer patients is broken. The CIK cells induced by PBMC in tumor patients are significantly reduced in both quantity and biological activity.

2.2. The changes of Tregs and MDSCs of NSCLC patients in peripheral blood

The response of the human immune system against tumors mainly depends on cellular immunity [42]. However, our immune system does not work effectively in the setting of malignancy. The reason for this may be the existence of immune suppression [60–62].

Tregs have an important role in suppressing adaptive immune responses and maintaining immune tolerance [63]. At the same time, the existence of Tregs may downregulate tumor-specific immunity. Tregs interact with various immune cell types, CD8⁺ T-cells [64], natural killer (NK) cells [65], and natural killer T (NKT) cells [66], thus, Tregs may have an important impact on cancer immune escape. Several studies have reported that the number of Tregs has increased in patients with NSCLC and other cancers [33, 67, 68]. It was reported that the percentage of Tregs was significantly reduced at week 2 after CIK cells treatment compared with the baseline and remained low at week 4 [51]. The decreasing of Treg was related with treatment cycle. Baodan Yu et al. found that significant reduction of Tregs frequency were presented in patients received with more than three cycles of CIK cells treatment compared with patients with less than three cycles of treatment [69]. In addition, inhibitory cytokines TGF- β as well as IL-10 were also decreased [51, 69].

MDSCs are heterogeneous population of myeloid cells known to exhibit potent suppression of T-cell proliferation and cytokine production [70–72]. Several evidence showed that MDSCs have a role in lung tumor growth and progression [73, 74]. In NSCLC patients MDSCs were reported in the peripheral blood [75, 76] and MDSCs were significantly higher compared with the healthy volunteers and were associated with poorer PFS [77]. In case of SCLC, preliminary results from a randomized phase II trial have shown that all-trans-retinoic acid (ATRA)-induced depletion of MDSCs may increase the immune response to DC-based vaccination to 42% [78]. Two Chinese articles found that CIK cells treatment can decrease the level of MDSCs in peripheral blood in malignant melanoma and gastrointestinal carcinomas patients. But, we did not find any literature to study the role of CIK cells on MDSCs in NSCLC patients.

2.3. The changes of immune cells of NSCLC patients in tumor tissue

A malignant tumor is not merely an accumulation of neoplastic cells, but also constitutes a microenvironment including endothelial cells, fibroblasts, structural components, and infiltrating immune cells that impact tumor development, invasion, metastasis, and outcome [79]. More recently, Fridman et al. reviewed that TILs was associated with clinical outcome in several cancers, including lung cancer [80]. All immune cell types might be found in a tumor such as CD4⁺ T-cells, CD8⁺ T-cells, macrophages, dendritic cells (DCs), mast cells, NK cells, memory cells, Tregs cells.

CD4⁺ T and CD8⁺ cells are the two major subsets of T lymphocytes and have different roles on tumor immunity within the tumor tissue [81]. Wakabayashi et al. [82] found that CD4⁺ T-cells but not CD8⁺ T-cells in cancer cell nests are associated with a better prognosis in NSCLC patients. Another study found that infiltrating CD8⁺ T-cells and CD4⁺ T-cells in NSCLC may work together to suppress cancer progression [83]. MDSCs were found in lymph nodes and tumor tissue of patients with NSCLC [84]. In mouse model, researchers found that CIK cells can inhibit the accumulation of MDSCs in the tumor [85]. But, we did not find any literature to study the role of CIK cells on infiltrating T-cells and MDSCs in patients with NSCLC. This may have been the result of the difficult access to tumor tissue, and relatively little research was done in vivo about the CIK cells, especially the studies published in high-level journals. Our research team may add these studies to their work in the future.

2.4. Immune checkpoint in NSCLC patients

In the setting of malignancy, immune suppression exists. Except the abovementioned aspects, immune checkpoint is another essential mechanism of immune suppression. These immune checkpoint included cytotoxic T lymphocyte antigen 4 (CTLA4), programmed death protein 1 (PD-1), lymphocyte activation gene 3 protein (LAG3), T-cell immunoglobulin domain and mucin domain 3 (TIM3), T-cell immunoreceptor with Ig and ITIM domains (TIGIT), and B and T lymphocyte attenuator (BTLA) [86]. They can inhibit the development and proliferation of lymphocytes [87]. These checkpoint expressed on T-cells was found in peripheral blood and tumor tissue have limited ability to effectively eliminate tumors, have gained considerable attention and PD-1 expression on peripheral blood T-cell subsets correlates with prognosis in non-small cell lung cancer [88, 89]. These molecules were found expressed on CIK cells [60]. The majority of these molecules, except BTLA were increased during CIK cells culture. But articles about the effect of CIK cells treatment on these molecules was very little in NSCLC patients, we only found one Chinese article found that after CIK cells treatment, the expression of PD-1 in peripheral blood decreased, and the decreasing was associated with the clinical stage of NSCLC.

2.5. Cytokines in NSCLC patients

In the process of ex-vivo expansion, cytokines play a decisive role in the differentiation and function of CIK. Only the addition of cytokines in vitro can induce peripheral blood monocytes (PBMCs) to differentiate into CIK cells. Importantly, different cultures affected the toxicity of CIK cells [15]. In the process of killing tumors in vivo, CIK can secrete a large number of

IL-2, IFN- γ , TNF- α , and GM-CSF and other cytokines. It can not only play an anti-tumor role directly, but also regulate the immune system of the body, and to stimulate cell proliferation and differentiation, and further enhance the cytotoxic activity of immune cells. Immune balance is controlled by the balance of cytokines produced by two distinct helper T-cell subsets, Th1 and Th2 cells [90, 91]. Our study found that the levels of IFN- γ following several treatment courses were significantly higher than the values observed prior to CIK cells treatment. The levels of IL-2, in vitro and in vivo, were elevated in CIK cells treatment group [12]. The serum levels of IL-4 and IL-6 in tumor-bearing patients were elevated after immunotherapy, and IFN- γ and IL-6 levels in patients with resected NSCLC were significantly increased. Otherwise, Li et al. have also shown that CIK cells treatment increased Th1 cytokines in patients who have no progression, but in patients who had developed metastasis had no change [92]. Successful immunotherapeutic interventions should overcome Th2 immunity by promoting and restoring antitumor Th1 immune response to achieve better clinical benefits [93].

3. Conclusion

In recent years, with the gradual clearer of tumor immunity regulation mechanism and the continuous improvement of gene transformation technology, tumor immunotherapy has been developed unprecedentedly. From the nonspecific immune stimulating agent to tumor vaccine, then monoclonal antibody and adoptive cellular immunotherapy for immune checkpoint blockade, therapeutic immune technology innovation provides more weapons for the human resistance tumor. Especially in the recent 5 years, with the rise of immunotherapy for immunological checkpoints and CAR-T-cell, immunotherapy has become more and more popular. Nonspecific immunotherapy, such as CIK, DC-CIK or NK cells, is widely used in China at present. These kinds of innate immune cells as the first immune defense cells, although the specific killing effect may be less than CAR-T, TCR-T, but these nonspecific cells play a positive role in lowering recurrence rate, improving tolerance of chemotherapy, improving life quality and prolonging the period of survival. However, the curative effect of recurrent and refractory tumors is limited to a small number of typical cases, and there is no evidence-based supports for prospective, randomized controlled trials. Besides, the combination of PD-1 antibody and CTLA-4 antibody is also easy to cause autoimmunity. The instability of tumor cells is also easy to form tumor heterogeneity. There is some progress in the research of CAR-T in the hematologic malignancies, but there are many problems in the treatment of solid tumors for CAR-T. Generally speaking, tumor immunotherapy is progressing faster and has many advantages. But if we want to apply for large-scale clinical application, we need to do a lot of research work.

Several articles had reported the safety and efficacy of CIK-cell therapy. Current studies on the immunomodulatory effects of CIK-cell therapy have focused on T lymphocytes and Treg in peripheral blood. It is much more challenging to study the relationship between CIK cells and immune system. Immune system is dynastic and complex, and a lot of other aspects are in the volume of the complex. The role of CIK cells on immune responses was associated with host factors. Not only cellular immunity we mentioned above but also humoral immunity get involved in tumor immunity. Tumor is characterized by distinct

individual differences, the same disease, different stages, and different pathological types, resulting in different outcomes. Immune system had important roles in these processes. Thus, we evaluate the immune function of the patient and analyze the status of each patient itself, which are significantly related to the final outcome. The ultimate goal of precision immunology for cancer is to select the patients who are most likely to benefit from a particular immunotherapy.

With the development of new technologies to dynamically detect the cancer-immune system interaction and at the same time taking into account the particularity of different groups of people, precision cancer immunology and the evaluation of immune function will be applied more widely, improving diagnosis and treatment of NSCLC patients.

Conflict of interest

No.

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