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Effect of Chemotherapy on Peripheral Blood DC Cells and Related Immune Cytokines in Patients with Non-Small Cell Lung Cancer

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Abstract

Objective: To analyze the effects of chemotherapy on peripheral blood DC cells and related immune cytokines (NKG2D, DC cells, TNF-a, IFN-r, HMGB-1) in patients with non-small cell lung cancer (NSCLC). **Methods:** Ninety-five NSCLC patients who attended the Oncology Department of the Affiliated Hospital of Chengde Medical College from September 2018 to February 2021 were selected as the research objects, and the changes in the expression levels of DC cells, NKG2D, TNF-a, IFN-r, HMGB-1 in the peripheral blood of patients at different time points (before chemotherapy, after the first chemotherapy, and after the second chemotherapy) were analyzed, and the correlation between DC cells in blood and NKG2D, TNF-a, IFN-r, HMGB-1 at each time point was explored. **Results:** The expression levels of NKG2D, TNF-a, IFN-r, and HMGB-1 in the peripheral blood of the patient before chemotherapy, after the first chemotherapy, and after the second chemotherapy gradually decreased, and there was no significant change in DC cells, except for DC cells at different times. The difference between each factor of each point was statistically significant (all $P < 0.05$). Pearson correlation analysis showed that there was no correlation between peripheral blood DC cells of patients at different time points and other factors. **Conclusion:** The decrease of other immune cytokines except DC cells in peripheral blood of patients with NSCLC after chemotherapy may be one of the mechanisms by which the patient's immune function is suppressed. There is no correlation between DC cells and other factors.

Keywords

Non-Small Cell Lung Cancer, Chemotherapy, NKG2D, TNF-a, IFN-r,

HMGB-1, DC Cells, Immune Cytokines

1. Introduction

Lung cancer, as the most common disease in the spectrum of malignant tumor diseases, its mortality rate is also among the top. Its causes are mainly due to the timeliness of inspection methods and the limitations of treatment methods. On this basis, the cure rate of lung cancer is lower than 20% of patients with advanced lung cancer who lose the opportunity for surgery, and the cure rate is even lower than 5% [1] [2]. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for about 80%. Due to its high invasiveness, insidious symptoms, difficulty to find, and lack of specific examination methods, most NSCLC patients have reached the middle and advanced stages when they are found to be sick, and a large part of them have lost the opportunity for surgery [3] [4]. The main treatment method for this type of patients is a differentiated chemotherapy regimen tailored to different individuals, but the side effects of chemotherapy are extremely large, and every patient, receiving chemotherapy, has a more or less reduced quality of life due to its side effects. The above facts have stimulated the research enthusiasm for tumor treatment methods, reducing the side effects of chemotherapy and improving its anti-tumor effect are the main demands of new treatment methods. In recent years, the advancement and gradual application of immunotherapy have brought some optimistic changes to the treatment of tumors, but its research is still not thorough and there is no immediate effect, and its research still needs to continue to work hard.

Immunotherapy mainly acts by stimulating the immune factors in the human body. In order to explore the relationship between chemotherapy and various immune factors and the relationship between each immune factor, we have conducted related studies. The report is as follows:

2. Object and Method

2.1. Basic Information

We took NSCLC patients from the Oncology Department of the Affiliated Hospital of Chengde Medical College from September 2018 to February 2021 as the research object, including 53 male patients and 42 female patients; the oldest is 77 years old, the youngest is 31 years old, and the average age is (60.17 ± 7.65) age; lung cancer type: 26 patients with squamous cell carcinoma, 61 patients with adenocarcinoma, and 8 patients with adenosquamous carcinoma; TNM staging (T stands for primary tumor, N stands for lymph node, M stands for distant metastasis): Stage III 28 patients, 67 patients with stage IV; KPS score (according to the patient's ability to take care of themselves, using a percentage method): 12 patients with 60 points, 21 with 70 points, 28 with 80 points, 23

with 90 points, and 11 with 100 points name.

Inclusion criteria: 1) Patients who were clearly diagnosed as NSCLC by pathology. 2) Patients between 18 - 80 years old. 3) Patients who have lost the opportunity for surgery after the assessment of the expertise in surgery, imaging, and pathology. 4) Patients whose survival period exceeds 3 months. 5) No contraindications to chemotherapy.

Exclusion criteria: 1) Patients with surgical indications requiring surgery. 2) Combined with serious basic diseases, such as immune system, severe dysfunction of head, heart, lungs and abdominal organs, severe infection, blood system diseases, etc.

All research subjects were approved by the ethics committee of the Affiliated Hospital of Chengde Medical College and were enrolled and signed an informed consent form.

2.2. Chemotherapy

The chemotherapy regimen is cisplatin/carboplatin + pemetrexed/gemcitabine/paclitaxel. Dosage: pemetrexed 500 mg/m^2, gemcitabine 1250 mg/m^2, paclitaxel 175 - 200 mg/m^2, cisplatin 75 mg/m^2, carboplatin AUC = 6, intravenous drip administration, 21 days as a cycle [5].

2.3. Research Methods

All patients were treated with chemotherapy on the day of chemotherapy (defined as the control group), after the 22nd day of the first chemotherapy (defined as the experimental group A), and after the 22nd day of the second chemotherapy (defined as the experimental B group), 30 ml of upper limb venous peripheral blood was drawn in the morning on an empty stomach, and left standing at room temperature. After 2 hours, the heart was separated at 1000 rpm for 20 minutes (centrifugal radius 14 cm), and the supernatant was taken and placed in a refrigerator at −80˚C for later use. The enzyme-linked immunosorbent assay was used to detect the levels of NKG2D, TNF-a, IFN-r, HMGB-1, and DC cells in the serum. Each factor detection kit was purchased from Kangtai Heyuan Biotechnology Co. Ltd. (Beijing).

2.4. Statistical Analysis

The data analysis of this study was carried out using SPSS 22.0. The measurement data conform to the normal distribution and are expressed by the mean ± standard deviation, and the t-test is used, the measurement data is the χ^2 test, and the Pearson correlation is used to analyze the correlation between DC cells and NKG2D, TNF-a, IFN-r, HMGB-1 at each time point sex. All P values are two-sided tests, and the test standard is $\alpha = 0.05$, and $P < \alpha$ is statistically significant.

3. Results

1) The expression levels of NKG2D, TNF-a, IFN-r and HMGB-1 in the peri-

pheral blood of patients before chemotherapy, after the first chemotherapy, and after the second chemotherapy gradually decreased, and there was no significant change in DC cells, except for DC cells at different times The difference between each factor of each point was statistically significant (all $P < 0.05$). See Table 1 for details.

2) Pearson correlation analysis showed that: at different time nodes (before chemotherapy, after the first chemotherapy, after the second chemotherapy), the peripheral blood DC cells of patients had no correlation with other factors. See Table 2 for details.

Table 1. Comparison of the expression of each factor between the experimental group and the control group.

Immunocytokine	Control group	Experiment Group A	Experiment Group B	t value	P value
IFN-r	1.34 ± 0.214	0.85 ± 0.20		7.209	0.001
IFN-r	1.34 ± 0.214		0.39 ± 0.192	16.011	0.001
IFN-r		0.85 ± 0.20	0.39 ± 0.192	11.547	0.001
DC cell	1.59 ± 0.239	1.51 ± 0.214		1.231	0.222
DC cell	1.59 ± 0.239		1.55 ± 0.212	0.387	0.700
DC cell		1.51 ± 0.214	1.55 ± 0.212	0.930	0.355
HMGB-1	66.95 ± 6.504	57.52 ± 4.392		9.117	0.638
HMGB-1	66.95 ± 6.504		43.49 ± 4.364	20.662	0.135
HMGB-1		57.42 ± 4.392	43.49 ± 4.364	14.581	0.375
TNF-a	9.04 ± 0.848	5.47 ± 0.644		16.035	0.001
TNF-a	9.04 ± 0.848		3.35 ± 0.646	30.566	0.001
TNF-a		5.57 ± 0.644	3.35 ± 0.646	79.007	0.001
NKG2D	2.04 ± 0.262	1.65 ± 0.127		8.727	0.001
NKG2D	2.04 ± 0.262		1.45 ± 0.136	13.197	0.001
NKG2D		1.65 ± 0.127	1.45 ± 0.136	7.279	0.001

Table 2. Correlation between DC cells and various factors at each time node.

parameter	DC cell (T1)		DC cell (T2)		DC cell (T3)	
	r	*P*	*r*	*P*	*r*	*P*
TNF-α	−0.036	0.754	0.039	0.773	−0.254	0.094
IFN-γ	0.067	0.7	−0.001	0.992	0.278	0.066
NKG2D	0.105	0.437	−0.083	0.529	0.035	0.715
HMGB-1	0.099	0.505	0.177	0.228	−0.084	0.562

4. Conclusion

After chemotherapy, the peripheral blood of NSCLC patients except DC cells decreased in other immune cytokines, which may be one of the mechanisms by which the patient's immune function is suppressed. There is no correlation between DC cells and other factors.

5. Discussion

As mentioned above, the treatment of tumors is currently in a bottleneck. Existing treatment methods cannot effectively control the occurrence and development of tumors, and after treatment, there will be more serious complications due to its side effects, which affect the quality of life. The development of oncology science is gradually developing towards the internal environment and the body's autoimmunity, and how to stimulate the human body's environment and autoimmunity in the process of anti-tumor therapy is particularly important [6] [7].

At present, immunotherapy has become a new treatment method for tumors. It mainly stimulates the body's immune factors to enhance the body's immunity, and then stimulates the body's own anti-tumor ability [5] [8] [9]. Compared with the broadly targeted and strong side effects of chemotherapy, immunotherapy has stronger specificity and smaller side effects, and the impact on the quality of life of patients is correspondingly reduced. Therefore, research on immunotherapy has attracted much attention. However, at present, immunotherapy needs to cooperate with chemotherapy to act on the human body, because the efficacy of immunotherapy is not exact, mainly because the research on the human body environment and various immune factors is not thorough enough. Due to the extensive targeting of chemotherapy, it kills tumor cells and also destroys the body's own immune system. The impact of different immune factors is unknown. When chemotherapy and immunotherapy work together, the human body has a synergistic or antagonistic effect, or different timings have different coordination effects. The optimal timing of combination therapy is unclear [10] [11]. Therefore, it is more meaningful to study the changes of various factors before and after chemotherapy and their correlation.

TNF-α (Tumor necrosis factor-α/Tumor necrosis factor-α) is secreted and produced by macrophages, and TNF-α is produced when macrophages receive a human infection or need to generate related immune response signals [12]. Some literature reports that the importance of TNF-α is mainly reflected in the fact that TNF-α can directly act on the surface of tumor cells to inhibit or directly kill tumor cells [13] [14]. TNF-α can be divided into types, namely secretory type and transmembrane type. There are many studies and the main role of killing tumors is mainly secreted TNF-α. The purpose of in-depth research is mainly Secreted TNF-α is harmless to the human body while killing tumor cells [15]. The current research on TNF-α is relatively incomplete, and most of the research is about the change of this factor in tumor tissue after corresponding

treatment, but there is less research on this factor in peripheral blood.

HMGB-1 is a non-histone DNA binding protein, which mainly plays a role in the process of cell differentiation, migration and regeneration. However, studies have found that traces of HMGB-1 can be found during the occurrence and development of tumors [16]. The increased activity of HMGB can stimulate the activation and maturation of DC cells and T cells. Therefore, an in-depth study of the main activity path and conduction and combination modes of HGMB-1 can provide strong and beneficial evidence for anti-tumor therapy.

IFN-γ (Interferon-γ/Interferon-r) has a wide range of effects. It participates in coordinating the body's immune system to resist viruses, regulate body immunity and anti-tumor effects. It is secreted by T lymphocytes and can be activated when IFN-γ binds to its receptor Antigen presenting cells, thereby stimulating the activation of Th1 cells [17] [18] [19].

NKG2D is an active receptor that plays a key role in the human body. It belongs to the NKG2 family and is an important active receptor that mediates the killing effect of NK cells in the immune system. The particularity of NKG2D is that it can activate the relevant cells of the body's own immune system without the need for antigen-presenting cells to play a role to play an anti-tumor effect. Some literature reports that the NKG2D signaling pathway plays a role in the occurrence, activation and progression of a variety of malignant diseases, and this role may be indispensable [20] [21].

DC cells (Dendritic Cells, DC) are the most popular antigen-presenting cells in recent years. They were discovered by Canadian scholar Steinman in 1973. With the deepening of research, it was discovered that cells are the most powerful antigen-presenting cells in the human body. Show cells [22]. A large number of studies have shown that DC cells play an irreplaceable role in the body's immune response. Therefore, anti-tumor research is also closely related to DC cells [23].

Our research found that in the course of chemotherapy, as the cycle of chemotherapy increases, immune factors except DC cells are significantly reduced, indicating that chemotherapy has a negative effect on all immune factors except DC cells, so it is improved in the early stage of chemotherapy. The body's immune capacity and increasing immunotherapy are very necessary, and it can be said that it is the best time. At the same time, the mechanism by which DC cells are not affected is still unclear. Continued research is needed, but it is not excluded that DC cells participate in tumor-related channels and are continuously activated by tumor-related factors without being affected by chemotherapy. If DC cells can be found to participate in tumor response targets. There may be better anti-tumor therapies. At the same time, there is no correlation between DC cells and other factors, and further research is needed to prove that, after all, the human body is the product of a variety of internal environmental chemical reactions, and a single non-correlation does not mean that it is absolutely irrelevant. The shortcomings of this study are that the enrolled patients come from a

single center, the number of samples is small, and the chemotherapy cycle is still short, which may cause bias in the results. In the future, the sample size and the research cycle should be expanded to confirm this conclusion.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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