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UTILITY OF CIRCULATING TUMOR CELLS IN ENHANCING THE THERAPEUTIC STRATEGIES FOR NON-SMALL CELL LUNG CANCER

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Abstract: Metastasis and recurrence are regarded as core factors affecting the prognosis of malignant tumors. In the basic theoretical components of metastasis and recurrence, tumor cell groups use the circulatory system to transport to distant organs, just like seeds spread in the soil, forming metastases with characteristics similar to those of the original tumors. The metastasis theory vividly It clarified the metastasis channels of malignant tumors and pointed out that "seed" tumor cells, also known as circulating tumor cells, are the focus of tumor metastasis and recurrence, and have a reliable basis for clinical analysis. In recent years, circulating tumor cells (CTCs), as potential biomarkers of tumor biology and tumor metastasis, have aroused great enthusiasm among oncologists and have become a hot topic in tumor biology analysis. This article reviews the clinical value of circulating tumor cells in non-small cell lung cancer and its clinical analysis, especially the diagnosis and treatment of lung cancer.
Keywords: Non-small cell lung cancer; Circulating tumor cells; Liquid biopsy

1 DETECTION METHODS OF CIRCULATING TUMOR CELLS

Lung cancer is a key cause of cancer death worldwide. Its 5-year survival rate is only 15%. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer patients, and its core pathological types are squamous cell carcinoma and adenocarcinoma. However, there is currently no real-time detection method to monitor the progression and prognosis of NSCLC. In the past, oncological examinations generally relied on histopathology and imaging methods. Although histological examination is the gold standard for diagnosing tumors, it is difficult to monitor tumor progression in real time due to the inability to perform multiple biopsies and possible adverse consequences (such as spread along the puncture tube); and small metastases are more difficult to detect. Blood is a window reflecting human health information. At this stage, the common hematological testing methods for non-small cell lung cancer include non-small cell lung cancer (NSCLC) multi-tumor marker carcinoembryonic antigen (CEA) + cytokeratin-CYFRA21-1) + squamous cell carcinoma anti-cancer method. However, the clinical effect is not ideal. Still under further research.

1.1 Routine Detection Methods of Circulating Tumor Cells in Clinical Practice

Cancer is the main cause of death in humans, and lung cancer patients account for the majority. Tumor metastasis leads to death in lung cancer patients. Most lung cancer patients relapse after radical treatment, and even show signs of tumor metastasis in the early stages of the disease. The transfer link is the integration of many complex events. First, malignant cells at the edge of the primary tumor must first invade the basement membrane, then use blood vessels and lymphatic vessels directly or indirectly, and finally colonize and spread to distant organs and tissues, eventually forming metastases [1].
CTC refers to the release of tumor cells into the peripheral blood circulation by solid tumors or metastases either spontaneously or as a result of diagnosis and treatment. It is the core factor in postoperative recurrence and distant metastasis of malignant tumors, and is also a key cause of death in cancer patients. The detection of circulating tumor cells (CTCs) in peripheral blood is of critical significance for early diagnosis of tumors, disease monitoring, and prognosis evaluation. To sum up, the focus of CTC detection technology is on the enrichment and identification of cells, which usually covers the following aspects [2]: (1) Cell search system based on surface antigens and immunofluorescence, but due to epithelial-mesenchymal transition The emergence of CTC, its positive rate in patients with advanced lung cancer is only 32%; (2) Methods based on cell size differences and filtration, such as membrane filtration separation of tumor cells, have the advantage of not relying on surface antigens of CTCs. , maintaining the CTC morphology and activity. However, the purity of the obtained CTC is relatively low, even less than 10% [3], and it is easy to lose CTCs with relatively small diameters; (3) The detection method based on DNA/RNA is very sensitive, but slightly Contamination can easily lead to false positive results, and the lack of specific markers greatly limits its clinical use. Therefore, at this stage, no method

has been found that is routinely suitable for detecting CTCs in the peripheral blood of patients with non-small cell lung cancer [4].

1.2 Quantitative Analysis of CTCs Based on Molecules

In many cancers, folate receptors (FRs) are highly expressed. Among them, FR-" expression has strong tissue and tumor specificity, and is highly expressed in lung cancer cells, especially non-small cell lung cancer cells, and is almost Not expressed in healthy human blood cells, it is an ideal CTC detection target for non-small cell lung cancer. Screen high-affinity ligand molecules targeting FR-" and couple the ligand molecules to oligonucleotides that can be detected by PCR To constitute a "ligand-oligonucleotide conjugate" probe. During detection, the conjugated probe is incubated with the sample containing CTC to completely bind to the surface receptor of CTC. The bound probe molecules are then washed with a specific eluent, and the eluted probe molecules are detected using quantitative PCR amplification to quantify CTCs. In this way, one CTC is amplified into at least 500,000 surface receptor molecules, and then fluorescence quantitative PCR is used to amplify and amplify 500,000 molecules to achieve the detection of rare CTCs [5]. This is how the human circulating tumor cell detection kit works. This kit combines the high acquisition rate of CTCs by the immunomagnetic bead negative sequencing method and the high sensitivity of nucleic acid detection technology, and has huge detection advantages [6].
The advantage of CTCs detection is that it can quantitatively count CTCs, measure multiple parameters, and analyze and classify cells simultaneously. Flow cytometry (FCM) combined with (IMS) enrichment separation and detection of cancer cells can significantly enhance the sensitivity of FCM detection [7]. The analysis results of Grosse et al. showed that the breast cancer cell line BT-20 and ordinary healthy human peripheral blood mononuclear cells (PBMC) were mixed at a gradient ratio and labeled with monoclonal antibodies containing cytokeratin and leukocytes, using multi-parameter Flow cytometry can significantly improve detection sensitivity. Specific antigens with four different wavelength fluorescent dyes. Although the FCM detection method is relatively simple, accurate and sensitive, and can quantitatively detect the peripheral blood of breast cancer patients, it is necessary to use microscopically specific ICC due to its inherent morphological defects. Stained chip (CTCs-chip.) to detect CTCs. The chip consists of 78,000 micropillars coated with anti-epithelial cell adhesion molecule (EpCAM) antibodies [8].

2 ANALYSIS OF THE CLINICAL RESEARCH VALUE OF CIRCULATING TUMOR CELLS

2.1 Prediction of Early Metastasis and Assessment of Prognostic Value

In early stages of cancer progression, local lymphatics are more susceptible to invasion than blood vessels. Lymph node metastasis will eventually enter the blood circulation to form circulating tumor cells, leading to the tendency of the primary tumor to metastasize throughout the body, and the primary tumor may have systemic metastasis. is defined as the “leukemic phase” (LP) of solid tumors. According to relevant analysis, the presence of tumor cells in the peripheral circulation is a reflection of the poor prognosis of cancer patients [9]. Therefore, detecting circulating tumor cells in non-small cell lung cancer is of critical significance for predicting early metastasis and assessing prognosis.

2.2 The Value of Monitoring Recurrence and Improving Survival Rate

90% of cancer-related deaths are caused by metastasis. Early detection of distant metastasis is an effective measure to improve the cure efficiency of lung cancer and improve the prognosis. Currently, more than 80% of lung cancer patients are diagnosed at an advanced stage, and for some other patients, although they are diagnosed at an early stage, metastasis and recurrence of the primary tumor occur very early after surgical resection, suggesting the presence of imaging findings for early staging. Lung cancer patients may not be able to "see" micrometastases. The analysis pointed out that CTCs are closely related to occult micro-metastasis of lung cancer, are the basis of distant metastasis of lung cancer, and are an important process in the formation of metastasis. Literature analysis pointed out that the detection rate of CTCs in 17 cases of localized small cell lung cancer was 52.9% [10]. Systemic spread of CTCs is an early event in the development of lung cancer. The detection of CTCs can help identify potential high-risk metastasis and recurrence patients at an early stage, optimize the follow-up of corresponding patients, and select reasonable treatments to reduce the incidence of lung cancer metastasis.

3 ANALYSIS OF CLINICAL APPLICATION OF CIRCULATING TUMOR CELLS

3.1 Guide Clinical Diagnosis and Staging

At present, the diagnosis and staging of lung cancer generally rely on imaging or pathological examination. The impact of tumor cell micrometastasis on patient treatment and prognosis cannot be accurately reflected. Compared with previous radiological assessment methods, circulating tumor cell counts can better predict survival time in patients with advanced non-small cell lung cancer. Relevant literature reports that circulating tumor cell counts can reflect the disease status of patients with non-small cell lung cancer [11]. Patients with non-small cell lung cancer treated with platinum-containing chemotherapy may have greater reductions in the number of circulating tumor cells than with single-agent chemotherapy. Compared with conventional radiological examination, circulating tumor cell count in patients with stage IV non-small cell lung cancer can better predict survival rate [12].

3.2 Assess the Risk of Metastasis and Recurrence

CTC levels are associated with distant tumor metastasis. The median baseline CTC levels of 51 SCLC patients with 0, 7.5, and >2 organ metastases were 2.0, 7.5, and 21.0, respectively. The number of CTCs in the liver metastasis group (64) was significantly higher than that in the non-liver metastasis group (3), P=0.0007, and was significantly correlated with the number of metastases, R=0.72, P<0.01. It is suggested that CTCs may be potential screening indicators for lung cancer metastasis. CTC detection was performed on 47 lung cancer patients. The results showed that the positive rate of CTCs in relapsed patients (83%) was higher than that in newly treated patients (78%), suggesting that CTCs may be related to the recurrence of lung cancer [13]. Relevant analysis pointed out that the detection rate of CTCs in the peripheral blood of patients with small cell lung cancer (SCLC) is relatively high (67% to 86%), and the CTC count greatly exceeds that of patients with non-small cell lung cancer. It is also determined that patients with small cell lung cancer are more likely to have hematogenous metastasis [14]. Therefore, detecting CTCs in the peripheral blood of patients with small cell lung cancer can provide early warning for disease metastasis and recurrence, thereby providing new basis for taking scientific treatment measures and improving patient prognosis.

3.3 Promote Efficacy Evaluation and Prognosis Judgment

The patient's treatment effect is related to prognosis and various factors. Many analyzes have shown that CTC detection plays a key role in predicting the response to chemotherapy and prognosis of lung cancer. Chemotherapy is currently the treatment of choice for small cell lung cancer. The efficacy is mainly determined by conventional imaging examinations, but it is difficult to judge the imaging manifestations of micrometastasis. A small clinical follow-up study found that the number of CTCs after chemotherapy was related to radiological response, suggesting that CTCs can monitor the effect of chemotherapy in lung cancer patients in real time [15]. Therefore, dynamic monitoring of CTC levels during treatment can provide evidence for monitoring the efficacy of disease treatment at the cellular level and selecting personalized treatment options.

Using the cell search system, 73% of 59 patients with small-cell lung cancer (SCLC) were positive for CTCs. The median survival time (157d) of the CTC number >215/7.5mL group was significantly lower than that of the CTC number <2 (729d) group. The CTC content of most patients decreased after 1 week of chemotherapy, suggesting that CTC can predict the efficacy and survival of patients with small cell lung cancer. Mr Ross et al. detected peripheral blood CTCs in 33 patients with metastatic non-small cell lung cancer. The results pointed out that CTCs could be detected in 36.4% of patients with metastatic non-small cell lung cancer. There is a difference in the effectiveness of chemotherapy between CTC-positive patients and CTC-negative patients. During chemotherapy, the progression rate of CTC-positive patients (66.7%) greatly exceeded that of negative patients (23.8%), P=0.02[18]. This proves that CTCs can be used as an effective indicator to predict the efficacy of chemotherapy in patients with metastatic non-small cell lung cancer. Relevant analysis pointed out that 85% of small cell lung cancer patients undergoing chemotherapy had CTCs in the peripheral blood. The median progression-free survival rate (PFS) reached 4.6% and 8.8 months, the overall survival rate (OS) reached 5.4% and 11.5 months, and the 1-year survival rate was 4.9% and 21.4% respectively. This demonstrates the baseline CTC number. It is an independent prognostic factor in patients with small cell lung cancer. Further analysis of the number of CTCs after 1 cycle of chemotherapy showed that the number of CTCs could not be reduced to 50, and the median overall survival rate OS was only 4.1 months [19].

Due to the heterogeneity of tumors, there is also an evolutionary process in the development of tumors. Metastases may have corresponding genetic changes compared with the original site. During the treatment process, the corresponding genotype and phenotype of the tumor also changed. Therefore, dynamic monitoring of tumor cells and changes in their genes is an urgent issue in personalized tumor treatment. The diagnostic value of this method for small cell lung cancer should be verified and studied in depth, as well as before and after surgery,

different stages of the disease, and recurrence. Disease dynamics related to changes in peripheral blood CTC levels during metastasis.

4 CONCLUSION

CTCs are associated with tumor recurrence and metastasis. The detection of CTC can help to gain a deeper understanding of the mechanism of tumor metastasis and bring new references for anti-metastasis treatment of tumors. Compared with lymph nodes and bone marrow, peripheral blood samples are easy to obtain, less invasive, and can be collected repeatedly. They are an ideal source for routine clinical trials and are considered "liquid biopsy specimens" rather than primary tumors. However, CTC detection still faces many difficulties in clinical use, such as the lack of specific tumor markers, the lack of consistent detection indicators, the inability to replace traditional imaging examinations, and the relatively high cost of detection. With the continuous improvement of CTC detection measures, many non-invasive CTC detection measures based on CTC sensitivity and specificity will be further developed, bringing new detection methods and new theoretical basis for the diagnosis and treatment of lung cancer.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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