

Peer Review File

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Reviewer A

Comment 1: Line 22. The authors state "However, the efficacy of the disease is not yet promising". I think what the authors really mean is that the results of treating the disease are not very successful, not that the efficacy of the disease is not promising. It's confusing.

Reply 1: Thank you for your kind advice. We have re-written this sentence according to the Reviewer's mentioned issue in the revised manuscript.

Changes in the text: However, the treatments of the disease need to be further improved.

Comment 2: Line 22. The authors state "Cell therapy has been shown to be a successful new treatment for lung cancer by an increasing number of scientific investigations". Despite how interesting and promising this therapy may be, I think the comment should be made conditional.

Reply 2: Thank you for your suggestion. We felt really sorry for our inappropriate expressions. We have made the corrections for more accurate expression,

Changes in the text: Cell therapy is expected to be a successful new treatment for lung cancer by an increasing number of scientific investigations.

Comment 3: Line 49. The authors state that the "5-year survival rate of patients with stage IA-IIB lung cancer after surgery can reach 53-92%, the patient's stage being strictly necessary due to the high surgical risk". I don't understand the second part of the sentence, which relates the stage of the patient to the high surgical risk.

Reply 3: We sincerely appreciate the valuable comments. We apologize for our incorrect statement. We have re-written this part according to your suggestion in the revised manuscript.

Changes in the text: 5-year survival rate of patients with stage IA-IIB lung cancer after surgery can reach 53-92%. However, the risk of surgery is high and surgery has certain requirements for the TNM classification of patients.

Comment 4: Line 52. The authors state "Radiotherapy is frequently used as an adjunctive treatment method in the operation, but it can lead to serious adverse reactions, such as decreased immunity and radiation pneumonitis". I do not understand the relationship between radiotherapy and the adverse side effect on immunity, taking into account that many authors associate its use with increased activity of the immune system (abscopal effect).

Reply 4: Thank you for pointing this out. The current research showed that radiotherapy can increase the infiltration of immune cell subgroups, and also through systemic immune response, which causes the extinction of radiological field tumors (abscopal effect) (1). Most of abscopal effect occurred in patients treated with immunotherapy combined with radiotherapy (2). In most cases, only radiotherapy is not enough to change the immune suppression of the microenvironment (3). On the other hand, radiotherapy also has certain immunosuppression (4). A recent study suggested that the tumor microenvironment changed dynamically after radiotherapy. The tumor microenvironment appeared as an activated state after radiotherapy initially, but over time it shifted to a suppressed state (5). Consequently, despite the

contributions of radiotherapy in cancer treatment, the subsequent shortcomings cannot be ignored at the same time.

Changes in the text: Radiotherapy is frequently used as an adjunctive treatment method in the operation, but it can lead to serious adverse reactions, such as decreased immunity and radiation pneumonitis.

Comment 5: Line 60. Again, "the efficacy of the disease is not yet promising". The authors refer to the treatment of the disease.

Reply 5: Thank you for your kind advice. We have re-written this sentence according to the Reviewer's mentioned issue in the revised manuscript.

Changes in the text: The treatments of the disease need to be further improved.

Comment 6: Line 65. I can't find the definition of the initials HSC.

Reply 6: Thank you for your reminder. We have added the definition of HSC.

Changes in the text: The majority of cell therapies are still in the early stages of development, with hematopoietic stem cell (HSC) transplantation being a proven method for treating hematological illnesses.

Comment 7: Line 125. "immune checkpoint. PD-L1 is upregulated in multiple tumors,⁶⁷ and can cause immune escape from the tumor". I think the number 67 appears by mistake.

Reply 7: Thank you for your careful reading. We were really sorry for our careless mistake. We added "is" and 67 has been removed in our revised manuscript.

Changes in the text: PD-L1 is upregulated in multiple tumors, and can lead to immune escape of tumor cells by binding to programmed death-1(PD-1) on T cells.

Comment 8: Line 154. The authors cite other researchers in capital letters, when previously it had been done in lower case. This event is repeated later (line 160).

Reply 8: Thank you for your reminder. In our resubmitted manuscript, we have made the corrections.

Changes in the text: Sam M. Janes and coworkers carried out phase I/II clinical trials of TRAIL transduced mesenchymal stem cells in lung cancer treatment, which is still in the experimental stage.

Qiaoling Chen's group prolonged the life span of the mouse Lewis lung carcinoma model by using MSCs expressing the pigment epithelium derived factor (PEDF).

Comment 9: In the bibliography, the way in which works are cited is not uniform. In some references the journals title is missing and in others the pages of the cited article.

Reply 9: We sincerely appreciate the valuable comments. We have checked the literature carefully and unified all the citations in the text.

Reviewer B

Comment 1: First, I feel their English grammar and the selection of words are sometime inadequate, leading to the difficulty to read their article. Please consult the expert person of

English-writing and receive their proofreading to refine the manuscript.

Reply 1: Thanks for your suggestion. We have carefully proofread and corrected the improper statements. The languages and expressions of our manuscript will be polished to be more native and accurate to reach the standards of the journal.

Comment 2: Second, I understand that they tried to summarize the study findings from many researchers, however, their manuscript seems like the simple enumeration of previous studies with use of many sentences. I recommend making some tables for each agent for the readability. I consider the tables summarizing the researchers' name, the publication year of each study, target molecular, results, and the feature of each study help readers to understand the contents of their manuscript.

Reply 2: Thank you for your suggestion. We made a table in the part of "conclusions", to show some studies of conventional treatments combined with cell therapy for lung cancer.

Changes in the text: The details were showed in Table 1 in a separate file.

Comment 3: In addition, I recommend the authors to revise the context considering the flow of the sentences in the manuscript. For example, they described the explanation of the CAR-T therapy and its efficacy in the lung cancer therapy from Line 84 to Line 129, however, just after these sentences, they described the insufficient antitumor activities of CAR-T in solid tumors from Line 130 to Line 138, which were contradictory explanations. I may construct the flow of this part as; the detailed explanation of CAR-T, then, explain the problem of CAR-T concerning to the insufficient antitumor activities, and then, show previous results from researchers showing 'low efficacy' (I consider the results showing some PR and many SD responses were not so effective) of CAR-T in NSCLC treatment, if I was the author of this manuscript.

Reply 3: Thank you very much for your constructive comments. Your suggestion really means a lot to us. In this article, we would like to summarize the advance of four cells in the treatment of lung cancer. These four cells are promising in the treatment of lung cancer, and many studies have confirmed their positive efficacy. In addition, there are still problems with cell therapy that deserve our attention. If these problems could be solved, it will be of great help to improve the efficacy and reduce the adverse side effects of patients. Therefore, the structure of our article is to introduce the basic situation of cells, summarize their effects on lung cancer, and finally put forward the urgent problems to be solved in a short space.

Reviewer C

Comment: The title of the article fully reflects the content of the review article.

In the "Abstract" section, the authors presented a brief description of lung cancer and the main treatment strategies for this disease. Separately, such a therapy strategy as cell therapy of lung cancer and diseases in which this treatment approach is effective (B-cell malignant neoplasms). In the abstract, the authors presented a general design of cell therapy with immune cells. In addition, it is indicated that lung cancer cell therapy needs to be improved. The purpose of this article "Achievements of cell therapy in lung cancer" is to analyze publications on a given topic to offer new prospects for the treatment of lung cancer based on cell therapy.

The "Keywords" presented in the article correspond to the content of the article and are

necessary.

This review article is divided into 3 main parts: «1. Introduction», «2. Cell therapy and lung cancer», «3. Conclusions». All sections are important and necessary.

In the section "1. Introduction", the authors characterized lung cancer, presented the latest data on morbidity, mortality and 5-year survival of patients with lung cancer. Information about the Chinese population of lung cancer patients is important and interesting. The section contains data on lung cancer treatment strategies: the positive and negative aspects of surgery, chemotherapy, radiation therapy, targeted therapy and immunotherapy are indicated. The authors point out that cell therapy is a new therapeutic approach that is gradually being applied to the treatment of lung cancer and there is some progress in these studies. The purpose of this review article was to discuss the theoretical basis, evidence, research status, development potential and current problems of lung cancer cell therapy.

The most important section is "2. Cell therapy and lung cancer". This section is represented by the following parts: "2.1 CAR-T", "2.2 Stem cells", "2.3 Cytokine-induced killer", "2.4 Tumor infiltrating lymphocyte". Initially, the authors provided information about the therapeutic method of cell therapy, while only one cancer (non-small cell lung cancer, NSCLC) is indicated, for which cell therapy is being successfully developed. In addition, the cells that are used in cell therapy (T cells, stem cells, killer cells, dendritic cells (DC), tumor infiltrating lymphocyte (TIL)) are indicated.

Further (part "2.1 CAR-T"), the authors presented information about the CAR-T technology and the therapeutic possibilities of such therapy. The successes of CART in the treatment of hematological diseases, targets for CART cells, side effects and difficulties in the treatment of solid tumors are indicated. The largest number of CAR-T studies is associated with lung cancer. The authors pointed out the reasons for the low efficacy and side effects of CAR-T in solid tumors: solid tumors rarely express specific tumor-associated antigens, immunosuppressive tumor microenvironment, limited persistence and impaired functions of CAR-T cells, CAR-T causes cytokine release (CRS) and neurotoxicity.

The part "2.2 Stem cells" presents data on stem cells and examples of SC cell therapy, as well as the mechanisms underlying the therapeutic effect. The main data related to MSCs and MSCs cell therapy. The positive quality of the article is that the authors presented not only the antitumor effects of MSC, but also described the negative effects of MSC therapy for lung cancer. These issues should be discussed and actively investigated.

In the part "2.3 Cytokine-induced killer", the authors pointed to the prospect of Cytokine-induced killer (CIK) cells cell therapy. CIK directly kill tumor cells and generally enhance the immune function of cancer patients, improve the prognosis of the tumor. The effectiveness of CIK therapy (for example, NSCLC) increases in combination with PD-1 blockade. The authors point out that patients receiving CIK should be aware of problems such as relapses, ineffective treatment and toxic effects.

In the part "2.4 Tumor infiltrating lymphocyte", the authors identified and discussed methods for obtaining Tumor infiltrating lymphocyte (TIL), the effects of TIL treatment (including when combined with nivolumab, tumor-specific antigen (TSA)) and side effects. in patients with metastatic malignant melanoma, NSCLC.

In the final section "3. Conclusions", the authors, using the results of other independent research groups, discussed the general provisions of the topic "Cell therapy of lung cancer", identified

problems that need to be solved and new treatment options using cell therapy. Of course, cell therapy is not a substitute for traditional treatments, but in combination with other treatment approaches can help eliminate some of their shortcomings.

The article is interesting, timely and important for clinical medicine. The text of the article is written clearly. All the drawings are well executed and complement the article, the captions to the drawings are clear. The manuscript did not cause any ethical problems. All links to publications in the "References" section are necessary and correct, made in the right style. Of the 80 links that are presented in the article, 50 links are from the last 5 years. I have no concerns about the similarity of this article with other articles published by the same authors.

Competing interests of authors do not create bias in the presentation of results and conclusions.

Reply: We sincerely thank you for your positive comments. Your nice words really encourage us to revise this manuscript carefully.