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Non-small cell lung cancer: news from immunotherapy

Abstract

This study examines the use of different vaccines and therapies for treating non-small lung cancer. The research is focused on immunotherapy to treat lung cancer that affects a large number of people globally. The research used literature review to gather data, and the results were examined thematically to present the most effective methods for treating this medical issue. The results of the study found that lung cancer can be treated effectively through different immunotherapy techniques.

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Introduction

The importance of the immune system in carcinogenesis has so far only been partially deciphered. The tumor microenvironment consists

1. immune cells,
2. stromal cells and
3. tumor cells.

Lymphocytes, in particular, develop their Macrophages via cytokine and chemokine cascades have complex and sometimes seemingly contradicting effects. The following scenarios are at the reaction of the immune system against the tumor possible:

1. Elimination of tumor cells
2. Promotion of tumor development through immunological factors.[1,2] This applies above all to established solid tumors since tumor surveillance is only effective to a limited extent there.

Even with non-small cell lung cancer (NSCLC), there are often dense infiltrates of the different T cell populations. The correlation with the prognosis is discussed controversially.[3] In a meta-analysis, the number correlates intratumoral T cells, however, positive with the Survival.[4] Because the immune system is so complex, immunological tumor therapy has long been considered hardly possible. Immunotherapy acts through an interaction between antigens and the immune system. The aim is to influence tumor growth through the body's own defense mechanisms. In the past decades has been - predominantly preclinical - intensively researched. A better and better understanding of the complex immunoregulatory mechanisms was the result. Currently, be various immune-modulating therapy approaches clinically developed.

Method

This study used a literature review-based research design to examine the data qualitatively. In this regard, various research articles relevant to the topic were studied, and the information was analyzed to produce the results. Therefore, using these methods, the following section presents different vaccinations and therapies for non-small cell lung cancer.

Results and Discussion

Vaccination

Target: The antigen-specific vaccination strategy is intended

1. The formation of tumor antigen-specific antibodies and
2. trigger cytotoxic CD4 and CD8 T cells,
3. sensitize the patient's immune system to specific tumor antigens and
4. Avoid mechanisms of tumor-induced tolerance.

Requirement: An important requirement for an effective presentation for this is one Tumor antigen through antigen-presenting Cells (dendritic cells, macrophages, B lymphocytes). Thus, they become tumor-specific T cells stimulated.[5] The triggering antigen should ideally be tumor-specific, differ from healthy cells; immunogenic effect; even in advanced disease, the Tumor cells remain detectable.[6,7]

L-BLP25

The liposomal BLP25 vaccine (LBLP25, tecemotide) is directed against the mucinous glycoprotein-1 (MUC1). This is usually expressed on the surface of mucin-secreting epithelial cells. In tumor cells, the protein is overexpressed or aberrant glycosylated.[8]A Phase II study initially yielded promising results. These could be used in a Phase III study (START) in 1513 patients; however, with inoperable stage III NSCLC not to be confirmed: L-BLP25 did not bring any significant survival advantage (median 25.6 vs.22.3 months; Hazard ratio [HR] 0.88; 95% confidence interval [CI] 0.75–1.03; p=0.123).[9] The vaccination was well tolerated except for mild flu-like symptoms and local inflammatory reactions.

Survival advantage of L-BLP25 vaccine

One Exploratory subgroup analysis showed that patients after simultaneous radiochemotherapy could benefit from L-BLP25 vaccination: median survival 30.8 vs.20.6 months; MR 0,78; 95% CI 0.64–0.95; p=0.016. According to a press release, however, a – currently still unpublished – randomized Japanese Phase I/II study for the same patient population after simultaneous or sequential chemotherapy also has no benefit for overall survival and progression-free survival.

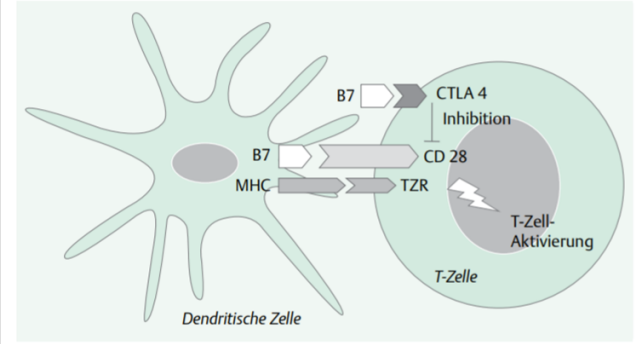

Figure 1 Role of CTLA-4.

MAGE-A3

Another vaccination approach is directed against the protein "melanoma-associated" antigen 3" (MAGE-A3). It is expressed almost exclusively by tumor cells and can detect in 24–50% of NSCLC cases.[6] A recently presented Phase III study (MAGRIT) evaluated 27 months of MAGE-A3 vaccination in 2272 patients with fully resected stage IB–IIIA NSCLC. All Participants expressed the antigen.[10] Compared to placebo, the vaccine was able to do not prolong disease-free survival in the overall population (median 60.5 vs.57.9 months; HR 1,024; 95% CI 0.891–1.177; p=0.74). The same was true for the subgroup of patients without adjuvant chemotherapy (median 58.0 vs.56.9 months; HR 0.970; p=0.7572).

Allogeneic tumor vaccines

Belagenpumatucel-L is an allogeneic tumor vaccine made from four different NSCLC cell lines. At to enhance immunogenicity, the cells are transfected with an anti-transforming growth factor β2 plasmid. A Phase III Study (STOP) tested a monthly maintenance therapy after first-line chemotherapy (radiation) therapy in NSCLC stage III or IV (n=532).[11] Median overall survival was not significantly prolonged compared to placebo (20.3 vs.17,8 months; HR 0.94; p=0.594). A subgroup analysis involved 305 patients in stage NSCLC IIIB/IV who were randomized within 12 weeks of chemotherapy. Here overall survival was prolonged with vaccination (median 20.7 vs.13.4 months; HR 0.75; p=0.083).

Further vaccination strategies

Various other approaches are in clinical testing.[12] These include, for example, vaccinations against gangliosides, vaccinations against the epidermal growth factor receptor (EGFR) or alternative vaccines against the above-described Antigens (e.B.TG4010).

Possible problems

It is possible that a T cell activation, even in the presence of potent antigens less pronounced – especially after repeated vaccination.[9] Other predictive markers could be necessary to define suitable patient collectives.

Checkpoint inhibitors

Principle of checkpoint inhibitors

In the regulation of the immune system, there are various elements that inhibit the immune response or co-stimulate so-called "checkpoints." The targeted inhibition of these checkpoint signals is intended to achieve an increased cytotoxic T cell response. Antibodies against CTLA-4 and PD-1 | The antibody ipilimumab is directed against the "cytotoxic T-lymphocyte antigen-4" (CTLA-4). He is already in melanoma and is for Time in an advanced clinical trial for use at NSCLC. Antibodies against the "programmed cell death protein" (PD-1) and its ligands also show first promising results.

The role of CTLA-4

The protein CTLA-4 is expressed on T cells. It is upregulated when antigen-presenting cells activate the T cell receptor complex. As a result, the Immune response attenuated.[7] Figure 1.

Chemotherapy with/without ipilimumab

A Randomized Phase II study was assigned to patients with untreated NSCLC to three therapeutic arms: carboplatin, paclitaxel and placebo carboplatin, paclitaxel and ipilimumab simultaneously/"simultaneously" (cycles 1 to 4) carboplatin, paclitaxel and ipilimumab delayed/"phasic" (cycles 3 to 6).

Delayed combination therapy

Concerning immune-dependent progression-free survival (irPFS), the ipilimumab chemotherapy combination of chemotherapy alone was only then significantly superior if it is delayed was administered (Table 1). Overall survival was also numerically better in the phasic group than in the simultaneous therapy group. (both differences are not significant).In addition, in the phasic group, the therapeutic effects were more pronounced in squamous cell carcinomas (irPFS, HR=0.55) than in non-squamous cell carcinoma (HR=0.82). The results are currently being reviewed in a phase III study (phasic application of ipilimumab carboplatin-paclitaxel vs. chemotherapy alone for squamous NSCLC).

Therapiegruppen-vergleich	medianes immun-abhängiges progressions-freies Überleben	medianes Gesamtüberleben
Ipilimumab-Chemo-therapie simultan vs. Chemotherapie	5,5 vs. 4,6 - HR 0,81 - p-Wert 0,13	9,7 vs. 8,3 - HR 0,99 - p-Wert 0,48
Ipilimumab-Chemo-therapie phasisch vs. Chemotherapie	5,7 vs. 4,6 - HR 0,72 - p-Wert 0,05	12,2 vs. 8,3 - HR 0,87 - p-Wert 0,23

HR: Hazard Ratio

The role of PD1 and PD-L1

PD1 is also a receptor on the surface of the T cell. He suppresses the immune response and intervenes in various regulatory mechanisms of the immune response (Figure 2).[10] Fibroblasts from the tumor stroma and also tumor cells themselves can Secrete ligands (PD-L1 and PD-L2) and thus change the immune response to the tumor. Various antibodies against PD-1 and PD-L1 are being investigated in clinical trials at NSCLC.

Nivolumab

In a large Phase I dose-finding study, 129 NSCLC patients after multiple pre-treatment nivolumab (1, 3 and 10mg/kg). The anti-

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PD-1 antibody was administered every 2 weeks for a maximum of 96 weeks or to the progression of the disease or to discontinuation in case of intolerance. In this prognostically unfavorable collective, an objective response rate of 17% was observed. The toxicity profile was acceptable.[10] In the 3 mg dose arm (this dose is given in further Phase II/III studies), median overall survival at 14.9 months, which One- and two-year survival rates at 56% and 45%.

Nivolumab in first-line therapy

Another Phase I study included different cohorts of chemotherapy naïve NSCLC patients (CheckMate 012). An interim evaluation showed a response rate of 30% (all patients) for nivolumab monotherapy with a sustained response in 67% of these patients at the Time of analysis.[11] Histochemistry suggests response | In both clinical trials, correlated strong immunohistochemical staining of membranous PD-L1 molecules on tumor cells with improved response and longer overall survival. However, the clinical activity of nivolumab has also been seen in PD-L1-negative Tumors observed. Nivolumab as a late line of therapy | A current Phase II study in 117 patients with squamous cell carcinoma showed for nivolumab as monotherapy in the 3rd century or later therapy line (CheckMate 063) a response rate of 15% (95% CI 8,7–22,2). The median overall survival was 8.2 months (95% CI 6.05–10.91).[12]

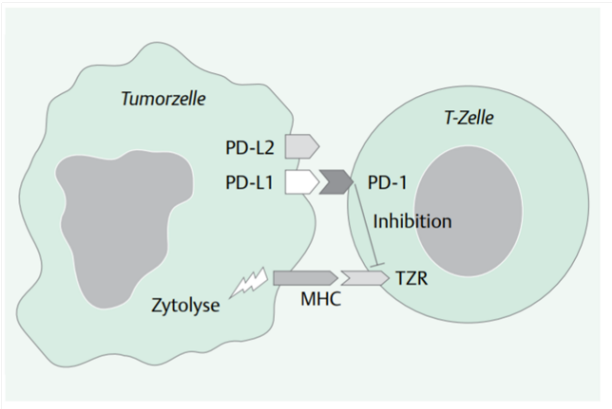

Figure 2 Regulatory mechanisms of the immune response.

Conclusion and future direction

In the end, it can be concluded that non-small cell lung cancer can be treated through various clinical therapies that include the use of various vaccines, as identified in this study. However, more research is needed in this area to determine the effectiveness of these vaccines. The current research relied only on qualitative research. In the future, the reliability and accuracy of the results can be further enhanced through the use of quantitative research.

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None.

Conflicts of interest

Authors declare no conflict of interest.

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