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Tg4010 Vaccine Targeting on NSCLC

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Abstract

Lung cancer is the most common factor of cancer-related deaths and about 85% of lung cancer is non-small cell lung cancer (NSCLC). MUC1, known as the attached protein or trans-membrane protein, is a kind of protein with highly glycosylation (greater than 50%) and high molecular weight (Mr>200*103). MUC1 is overexpressed in many malignancies, and as a tumor-associated antigens (TAAs), it exposes antigenic epitopes and potential T-cell targets. TG4010 vaccine, which encodes as MUC1 tumor-associated antigen and interleukine-2 and targets MUC1, is an effective and promising targeting strategy for patients with advanced NSCLC when in combination with first-line chemotherapy. This review is mainly aiming to focus on the evidence to clinical statistic data of different phases TIME trails for efficacy of TG4010 vaccine immunotherapy observed in NSCLC and some consequent thoughts.

Keywords: Non-small cell lung cancer; Vaccine therapy; MUC1; TG4010

Introduction

Primary bronchial lung cancer, also named as lung cancer, is one of the malignant tumor of which incidence and mortality increased year by year. Nearly for 50 years, the incidence of lung cancer increased significantly in Euramerican developed countries and some of the industries of Chinese big cities. The mortality rate of lung cancer in males has been in the lead, and also in females has increased rapidly, which is in 1st position among the common malignant tumors of females (**Figure 1**) [1]. Even though the related studies about lung cancer are countless, the effective novel treatment of lung cancer still needs to be continuously explored. Lung cancer is broadly divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), nearly 80%-90% patients with lung cancer belong to non-small cell lung cancer (NSCLC) (**Figure 2**) [2]. Surgical operation combined with radiation and chemotherapy treatment for patients with early staged NSCLC could improve their life quality and prolong their survival time [3]. However, most of patients with lung cancer have been at advanced period when firstly diagnosed [4], and for advanced lung cancer patients treated with radiation and chemotherapy, the 5-years survival rate after surgery is only 15% [5]. Utilizing the newer cytotoxic therapy to treat patients with advanced metabolic disease and adopting a new generation of small molecules targeting the epidermal growth factor therapy to deal with advanced carcinoma, the survival rate is also very low [6-8]. In recent years, a lot of researches, focusing on how cancer cells go against immune system and how to escape immune cells could break through the limitations of traditional cancer treatments and make new targeted active immune-therapies relapse [9-11].

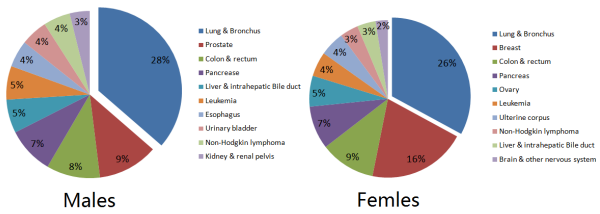

Figure 1 The different cancer type of estimated deaths by sex.

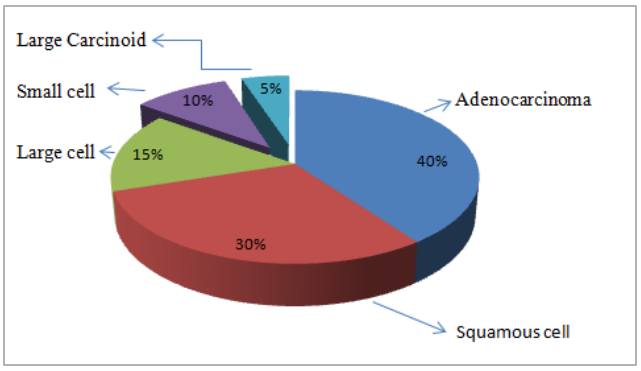

Figure 2 The type of lung cancer.

A vaccine against tumor-associated antigens (TAAs) may be a novel therapeutic strategy, and current researches about vaccine immunotherapy would represent much promising

perspective in the treatment of advanced lung cancer, not because targeted antigens of tumor cells change more selectively in order to resist mutate immune factors, but also because suppressive immunological microenvironment surrounding cancer cells forms progressively [12]. Immune inhibitors or vaccine to the immune system has been adjusted to provide important clues for the potential treatment of lung cancer, for example, using vaccine immunotherapy could successfully break through especial immune resistance in melanoma and castration-resistant prostate cancer, so to find a checkpoint is the key point [13,14]. In the past few years, the appearance of many anti-cancer vaccines promotes the progression of immunotherapy; some of them gained positive data in Phase II clinical trials, but failed in phase III trial without exception. However, recently TG4010 vaccine was reported to improve the overall survival (OS) greatly and remission rate, subgroup analysis showed better improvement of TG4010 on patients with lung squamous cell carcinoma or specific types of molecules in IIB/III TIME trail.

Vaccines targeting the pathogen is that the body's immune system identifies "non-self" foreign antigens to trigger the protective effect so that the immune response cascade occurs, which is often the highly effective defense measures for body, but currently clinical efficacy of cancer vaccine therapy is not optimistic. According to the diversity of the targeted tumor antigens, the characteristic of cancer vaccines is not limited to whole tumor cells, but also including DNA viral vectors, proteins or peptides, as well as defensive vaccine.

In order to make vaccine enhance immune response against cancer and conduct preventive function powerfully, the biomarkers should be recognized essentially. TG4010, which is developed with recombinant attenuated Ankara virus vaccine targeting MUC1, is one of the important vaccines against NSCLCs and genetically modified to encode MUC1 tumor associated antibody and full-length interleukin-2 [15]. Moreover, tumor MUC1 reveal new antigenic epitopes and potential T-cells targets. Additionally, over-expression of MUCI on the cellular surface in many malignancies being linked to worse prognosis could promote tumor cellular growth, cellular survival and metastasis. In this section reviews, we evaluate the therapeutic efficacy of the TG4010 vaccine by searching the recent related advances and claim that MUCI is one of the good antigenic targets for vaccine immunotherapy.

An Immunoassay Method for Detecting Pulmonary Immune Status

Immunotherapy, which could improve treatment tolerability and increase treatment efficacy after radiotherapy or chemotherapy, is a potential pathway to provide critical new checkpoint and improved therapeutic index [16]. However, the immune system in lung is formed of multiple parts, including abundant immune cells with a complex and precise cytokine network, and also including structural elements like mesenchymal cells and epithelial cells which have a essential but different roles. These elements integrate fixedly and the percentage of each immune cells is within a regular range when in normal conditions [17]. Bronchoalveolar lavage (BAL) fluid examination is a quantitative and well standard method to evaluate the lung immune status if in steady state or in morbid state [18-20]. Under local anesthesia with 2~3 mL 2% lidocaine, 100 mL~300 mL physiological saline is used for the lavage, the recovered fluid is analyzed to determine the differential cell count, total cell count and other cellular elements. The total cell count is nearly 10 million in the referenced BAL of normal state: the proportion of eosinophils is less than 1%, neutrophils less than 5%, lymphocytes less than 15%, and macrophages more than 80%, therefore, the cell viability reaches to more than 90% as standard, and this BAL diagnostic analysis is the significant method and could be applied at any stages of advanced lung cancer [18,20,21] when pulmonary immune status is evaluated.

Immunotherapy with a MUCI Vaccine (TG4010)

MUC1 is a mucinous transmembrane glycoprotein which has a large NH2-terminal extracellular domain with insufficient or abnormal glycosylation. Its peptide core epitopes are exposed to be used as tumor-associated neo-epitopes, with the shortened carbohydrate side chains. The Melanoma Associated Antigen (MAGE-A3) and the Membrane Associated Glycoprotein (MUC-1) are the two famous antigens of lung cancer and used to produce vaccine [22-24]. However, TG4010 vaccine, also named as MVA-MUC1-IL-2 vaccine, is born to target this MUC1 antigen [25]. And it could result in the activation of T-cell immunological responses through superficial antigenic epitopes of MUC1 [26]. In normal state, the function of MUC1 is associated with mucin formation, but high expression of MUC1 is greatly thought to be involved in migration of lung cancer cell, resistance to chemotherapeutic agents, escape immune system and resistance to stress-induced apoptosis [27], and also associated with poor prognosis in advanced adenocarcinoma [28,29]. Epithelial cells normally express MUC1, which is highly expressed on the surface of more than 80% tumor cells, including breast, multiple myeloma, prostate, and especially greater than 60% of NSCLC [30]. Additionally, because of over-expression of MUC1, the AKT pathway and the phosphatidylinositol 3-kinase (PI3k) pathway are activated, resultant cells proliferate greatly [31].

Preclinical Trail and Phase I Clinical Trail

In preclinical work, the study showed that peripheral blood mononuclear cells were got from these healthy donors carrying MVA-MUC1-IL-2, then by its transduction, MUC1 was induced to express on dendritic cell surfaces [32]. As is known, MUC1 is highly expressed on several maligancies including NSCLC, then the phase I clinical trial was conducted in various solid tumors. The performance status of patients from an Eastern Cooperative Oncology Group were 0-2, histologically showed tumor with higher than 50% expression of MUC1

tissue, and patients with incurable disease were also chosen for trial enrollment [33]. In two separate phase I studies, thirteen evaluable patients were injected with increasing doses of TG4010. TG4010 was conducted three dose cohorts, at least two were injected subcutaneously, once each 3 weeks for cohort 1 and cohort 2, weekly for cohort 3. Three of them enrolled had NSCLC. A patient with NSCLC was going on administration of five doses of TG4010, and the size of his metastases declined remarkably. Patients with metastatic tumors could tolerate the injections of TG4010 in this trial, and the safety of the product was observed, the dose of TG4010 was defined for further clinical trials [34]. Mild side effects after injection of TG4010 vaccine were as followed: 4 patients with injection site pain, 2 patients with influenza-like syndrome, 1 patient with rash and 1 patient with vertigo.

Phase IIB/III TIME Clinical Trail

In phase IIB part of the IIB/III TIME trial, TG4010 was investigated further in combination with the first line chemotherapy in patients with advanced non-small cell lung cancer and TrPAL biomarker in the setting. Previously untreated patients aged 18 years old or older with stage IV NCSLC with MUC1 expression higher than 50% of cancer cells and without a known activating EGFP mutation were recruited for trials, with at least 4 months life expectancy, more than one part measurable by CT-scan and a 0-1 PS (performance status) according to WHO (World Health Organization). Patients meeting the following criteria were excluded: 1, patients with advanced NSCLC had been treated with prior systemic therapies; 2, patients with concomitant brain metastases treated unsuccessfully or another malignancy with the past five years, in addition to the basal cell carcinoma of skin or epithelium and cervical cancer [35]. In a multicenter and randomized separate first phase II study including sixty-five patients with stage IIIB/IV MUC1-positive NSCLC, platinum-based chemotherapy (cisplatin/vinorelbine) (N=44) was administered in combination with TG4010 (108 plaque forming units injected subcutaneously weekly for six weeks, and then every 3 weeks) versus TG4010 mono-therapy until progression followed by the addition of chemotherapy (N=21) [36]. Two types of combination therapy were designed: Arm 1, simple TG4010-chemotherapy combination with cisplatin (100 mg/m day 1) and vinorelbine (25 mg/m day1 and day 8); Arm 2, a sequential protocol in which TG4010 was first administered as mono-therapy until disease progression, then followed by TG4010 plus the same chemotherapy as in Arm 1.The results showed that the combination group had a higher response rate than that in TG4010 group, with a numerically inferior median and 1-year survival rate. The combination of TG4010 with standard chemotherapy was generally well tolerated and feasible.

Furthermore, a larger open-label randomized phase IIB trial was initiated and reported in 2011 to test this hypothesis [37]. This study enrolled 148 patients with advanced (stage IIIB or IV) NSCLC highly expressing MUC1 by immune-histochemistry. Patients were divided randomly into two groups:74 patients who received TG4010 combinated with cisplatin(75 mg/m^2 on day 1) and gemcitabine (1250 mg/m^2 on days 1 and 8) repeated every 3 weeks for up to 6 cycles were in the combination group; Another 74 who received the chemotherapy alone were in the control group. In the TG4010 plus chemotherapy group, 6-month progressive free survival (PFS) was 43.2% while that was 35.1% in chemotherapy alone group. The objective response rate was 41.9% in the experimental group *versus* 28.4% in the control group; median OS of responding patients was better in the experimental group than that in control group: 23.3 months *versus* 12.5 months. The presences of activation markers for CD16+, CD56+, CD69+ cells which is the phenotype of activated NK cells (aNK), was analyzed as potential biomarker to predict safety and efficiency of TG4010 and the response to TG4010. Patients with normal level of this aNK cells at baseline level (73% of the evaluable population) demonstrated the better benefit. These results met the primary statistic end point of the study.

In another phase II study, TG4010 was used in renal clear-cell carcinoma to observe its efficacy and tolerability [38]. The clinical survival time and the duration of response between these two studies were similar, and also similar to other observation in patients with melanoma who received dacarbazine plus ipilimumab [39]. To observe the Health related Quality of life (HRQOL) influenced by TG4010 in patients (aged 18 years or older) with stage IIIb and IV NSCLC, a multicentric open label randomized clinic trial was designed in 148 patients with advanced non-small-cell lung cancer which over-expressed MUC1 [40]. This study achieved its secondary endpoint on the assessment of OS and HRQOL using the functional assessment of cancer therapy-lung (FACT-L) questionnaire. 148 patients were allocated randomly by 1:1 to two groups: in Arm 1, 74 patients were treated with TG4010 (sub-cutaneously at the dose of 108 pfu) plus chemotherapy one time every week lasting for 6 weeks and then one time every 3 weeks as the experimental group; in Arm 2, other 74 patients were treated with the same chemotherapy alone as the control group. In arm 1, 66 patients (89.2%) finished the FACT-/L questionnaire at baseline while 63 patients (83.8%) in arm 2 completed this. The median TUDD of physical Well-Being score with a 5-point MCID [31] or death among the 116 patients included (58 each arm) was significantly different: 65 days in arm 1 versus 86 days in arm 2. In arm 1, the median TUDD of Emotional Well-Being score with a 5-point MCID or death among 117 patients included (58 patients in arm 1 and 59 in arm 2) was 97 days lower than that in arm 2 (99 days), while TUDD of Functional Well-Being score among 116 patients included (58 per arm) in arm 1 was 92 days and also lower than that in arm 2 (99 days). And TUDD of lung cancer subscale score was 97 days in arm 1 *versus* 147 days in arm 2. In this trial, these results did not present that the statistical difference of TUDD of HRQOL score was apparent between this two strategic therapy which found the good efficacy and tolerance of TG4010 plus chemotherapy in patients with advanced NSCLC. A longer TUDD was observed in patients treated by TG4010 with normal level of aNK cells than that with a high level of aNK cells. Even though the benefit in term

of OS was not showed, 50% of trials had observed the changes in HRQOL [41,42].

To further observe the potentially predictive of TG4010 efficacy in combaination with first-line chemotherapy, the phase IIB part of the phase IIB/III TIME trial was conducted between April 10 in 2012, and Sep 12 in 2014. In this double-blind and placebo-controlled trial, 222 untreated patients with stage IV NSCLC were allocated into two groups randomly by 1:1: the TG4010 plus chemotherapy group and the placebo plus chemotherapy group. The hazard ratio (HR) for progression-free survival was indistinctive between patients with TrPAL values of less than or equal to the ULN and patients with TrPAL values of greater than the ULN, but in the former, 98.4% probability of the HR was less than 1, while 31.3% in the latter which did not met the endpoint. The statistical data determined the greater benefit in progression-free survival with TG4010 plus chemotherapy than with placebo plus chemotherapy. Additionally, TrPAL biomarker had its potential clinical value. The phase III part would be continued further. And it shows the progression of TG4010 on NSCLC in **Table 1**.

Table 1 TG4010 vaccine trail summary NSCLC.

Vaccine	Phase	Stage	Number/Status	Outcome Data
TG 4010	Pre	Peripheral blood mononuclear cells	Terminate	MUC1 was induced to express on dendritic cell surfaces
	I	All solid tumor	13/Terminate	1 patient with NSCLC respond against tumor
	II	IIIB/IV, combined with platinum-based chemotherapy	65/Terminate	OPR: 29.5%, TTP: 4.8 months MO.OS: 12.7 months
	IIB	IIIB/IV, combined with CDDP/Gemcitabine IV, combined with placebo chemo- therapy	148/Terminate 222/Terminate	ORR: 41.9% *vs.* 28.4% (control) 6-MO.PFS 43.2% *vs.* 35.1% HR for PFS: 98.4% less than 1 *vs.* 31.3% (control)
	III	IV, MUC1 positive	1000/Ongoing	NA

Conclusion and Future Perspectives

Recently, numerous clinical trials are conducted to explore the efficacy and tolerance of vaccine immunotherapy in therapeutic treatment of lung cancer. Antigen-specific vaccines have met the primary endpoint and also, immune-modulatory agents regulate the function of T cells and B cells, affecting the complex anti-tumor immune response. The vaccine therapy in combination with other therapeutic options would be the major way against tumors in the future [43,44]. Furthermore, therapeutic treatment in the future will challenge the tolerance of initial treatment and identification of immunotherapeutic biomarkers [45].

The combination therapy is the significant direction and becoming the common approach in anti-tumor therapy. In the view of the statistic dates of clinical trials, combinations between different therapies are more valid and beneficial than single targeted therapy against non-small cell lung cancer [46]. It is becoming clear that vaccine immunotherapeutic strategies has promising perspectives in the future to treat lung cancer, and the randomized phase III clinical trials comparing TG4010 vaccine plus other cytotoxic therapies with standard chemotherapy would be ongoing internationally to determine whether TG4010 vaccine therapy could generate meaningful improvements in progression-free survival, inerratic tolerance and median overall survival and elevate whether it could gain the best benefit in federal treatment so that the best time could be determined to administer a patient's treatment schedule [47,48]. From the trails, MUCI is one of the good antigenic targets for vaccine immunotherapy. Absolutely, clinical efficacy of TG4010 vaccine combinational therapy is still disappointing. Furthermore, the illumination of predictive biomarkers of response to better select patients who would obtain most benefits from immune-therapies is utmost significant, and toxicity would be limited to patients who could not respond [49]. As is known, the lung is a largely sophisticated organ and has elaborate immune environment, so breaking the tolerance to specific cancer-associated antigens is the burdensome checkpoint [50]. Radiotherapy or chemotherapy has the synergetic effects with vaccine immunotherapy on treating advanced NSCLC, but the efficacy for distant metastatic NSCLC needs to be closely observed. In addition, the mechanisms of the occurrence, development and metastasis in lung cancer are very complex, and the body's genetic mutations could result in the appearance of lung cancer stem cells, competing against humoral immune systems. Formation and existence of resting cancer stem cells makes it difficult for lung cancer to be treated absolutely, even result in tumor metastasis by relative resistance to radiation therapy and chemotherapy [51,52]. It is so essential for vaccine immunotherapy combining with other therapies to target CSCs. More importantly, the insufficiency of current immuno-therapies is failed for treatment, because CSC population forms and exists so that current immuno-therapies directly confront tumor differentiated antigens from differentiated cancer cells rather than the CSC populations which lack these antigens and express different antigens from the differentiated tumor cell antigens. Therefore, newly emerging novel approaches may manifest a challenging promising future and newly TG4010 vaccine may appear to breakthrough barriers and achieve more comprehensive outcomes.

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