Vaccination therapy for non-small-cell lung cancer: review of agents in phase III development

L. Decoster, I. Wauters & J. F. Vansteenkiste*

Respiratory Oncology Unit (Pulmonology), Leuven Lung Cancer Group, University Hospital Gasthuisberg, Leuven, Belgium

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The historical results of cancer vaccination for non-small-cell lung cancer (NSCLC) were disappointing. In the current decade, however, new insights in the interaction between tumours and the immune system have led to the development of immunotherapy as a fundamentally new concept for the treatment of NSCLC. Modern NSCLC vaccine strategies rely on better identification of antigenic targets, addition of strong immunoadjuvants, and use of more efficient delivery systems. These treatments have convincingly demonstrated to elicit potent immune responses and have shown promising efficacy signals and excellent tolerability in phase II randomised studies. This—together with recent positive phase III data in indications other than NSCLC—has helped to establish the proof of principle for cancer vaccination. In NSCLC, ongoing phase III trials are investigating this approach in different treatment settings: the Melanoma AntiGen A3 vaccine in resected early-stage NSCLC, the L-BLP25 vaccine in locally advanced NSCLC after chemoradiotherapy, and belagenpumatucel-L, the epidermal growth factor and the TG4010 vaccine in advanced stage, either as an adjunct to chemotherapy or as maintenance after completion of chemotherapy. Mode of action, development, available clinical data, and currently ongoing phase III studies are reviewed.

Key words: cancer vaccines, clinical trials phase III, immunology, non-small-cell lung cancer, review

introduction

Non-small-cell lung cancer (NSCLC) accounts for ~85% of all lung cancer cases. Many of these patients present with metastatic disease at the time of diagnosis. A treatment with radical intent can be offered to patients with non-metastatic stages, but even then, a large number of patients will relapse and die of their cancer, illustrating the need for novel therapeutic options.

Recent improvements in systemic therapy are the new treatment paradigms with maintenance chemotherapy [1] and the use of targeted therapies in tumours selected by molecular biological characteristics [2]. Another innovative strategy that may improve overall survival (OS), with reduced toxicity compared with conventional cytotoxic chemotherapy, is the use of therapeutic cancer vaccines.

Historically, immunotherapy for NSCLC was rather unsuccessful, because effective immune responses were hard to achieve. Major steps forward in the last decade were the identification of relevant target antigens and the development of adjuvants and delivery systems able to circumvent the immune-suppressive environment of NSCLC [3]. Several new approaches have now entered phase III clinical trials in all stages of NSCLC. The possible clinical impact of these different vaccination strategies is updated here.

cancer immunology

Over the past decade, it has become clear that the immune system is able to recognise malignant cells as foreign, as these cells may express specific tumour antigens [4]. In a process known as immune surveillance [3], an immune response is mounted against such cells, possibly leading to their elimination. An illustration of failure of this mechanism is the increased incidence of malignancies seen in heart and lung transplant patients under immunosuppressive therapies [5].

A normal cellular immune response against tumour cells begins with the uptake of tumour antigens by antigen-presenting cells (APCs) such as dendritic cells (DCs) and macrophages (Figure 1). These cells subsequently process the antigens and display them on their surface in association with the major histocompatibility complex (MHC) class I and class II. In the presence of the required co-stimulatory signals (such as B7.1 and B7.2), different subtypes of immune effector cells may become activated.

CD4+ T helper cells augment the immune response by secreting interleukins (ILs) 2 and 12 and interferon gamma, which enhances the activation of CD8+ T cells into cytotoxic T lymphocytes. The latter recognise the antigens on tumour cells, which leads to the initiation of different processes, such as the release of pore-forming granymes and perforins, resulting in apoptosis of the tumour cell (cellular immune attack) [3]. Furthermore, activated CD4+ T cells enhance the killing activity of natural killer cells, as well as the phagocytic activity of macrophages.
Activated CD4+ T helper cells also stimulate B cells, which leads to their maturation into plasma cells, with production of antigen-specific antibodies (humoral immune attack).

However, tumours also develop different evasive strategies that lead to a condition of immunotolerance. Regulatory T cells secrete cytokines such as transforming growth factor beta (TGF-β) and interleukin 10, which interfere with migration of DCs and their maturation into effective APCs and which block the actions of macrophages and natural killer cells. A tumour may also induce downregulation of antigens, MHC molecules, and co-stimulatory molecules, which impedes T-cell recognition and activation. Finally, tumour cells may fail to activate mechanisms involved in apoptotic cell death, making them resistant to the effect of cytotoxic T cells [7].

cancer immunotherapy

Different strategies have been developed to aid the immune system elicit an effective response against evolving cancers. The term cancer immunotherapy covers any interaction with the immune system to treat cancer and three fundamentally different approaches can be distinguished.

First, there is ‘supportive’ immunotherapy, i.e. non-specific enhancement of the innate immune system. Historical examples of this strategy are Bacillus Calmette-Guerin [8] and levamisole [9], or interferons and interleukins [10]. None of these proved to be beneficial. More recently, two large phase III studies in patients with advanced NSCLC with PF-3512676 (ProMune®, Pfizer, New York, NY)—an agonist of the toll-like receptor 9 that enhances maturation of DCs—were stopped prematurely because of lack of efficacy and safety issues (sepsis and thrombocytopenia) [11, 12]. Two ongoing phase III studies are investigating the potential benefit of the oral immunomodulatory agent talactoferrin alpha—a recombinant human lactoferrin—acting by DC recruitment and activation in the gut-associated lymphoid tissue [13]. Ipilimumab—an immunomodulating monoclonal antibody (mAb) acting on the cytotoxic T lymphocyte antigen 4—improves OS in patients with metastatic melanoma [14]. At the ASCO 2010 congress, improvement of progression-free survival (PFS) with this agent was also reported in a phase II randomised study in advanced NSCLC patients undergoing first-line chemotherapy [15], and further phase III testing in lung cancer has been planned.

The term ‘passive’ immunotherapy covers any passive supply of immune response agents to the body, such as cytotoxic T cells, or antibodies such as cetuximab. The latter are usually called targeted therapy.

In ‘active’ immunotherapy, there is specific priming of the host immune system to recognise the tumour as foreign and to augment antitumour T1-type CD4+ helper and CD8+ cytotoxic lymphocytes, thus turning the immunosuppressive environment into an immunostimulating environment. The latter strategy is vaccination in the true sense of the word and its use in NSCLC is the topic of this overview.

therapeutic cancer vaccination in NSCLC

The initial results of vaccination trials for NSCLC were disappointing and NSCLC was long considered a poorly immunogenic tumour. The ideal NSCLC vaccine should therefore be able to elicit both potent CD4+ and CD8+ T-cell responses whilst circumventing the mechanisms of tumour-induced immune tolerance. Furthermore, the vaccine should be as tumour specific as possible to avoid normal host cells being targeted. To achieve this, a vaccine should consist of antigens that are unique to cancer cells (tumour-specific antigens) or antigens that are expressed differently than in normal cells (tumour-associated antigens) [3]. The vaccine must also contain a strong adjuvant to potentiate the immune response and a delivery system for improved antigen presentation and activation of the immune cascade. The lack of these characteristics may have been responsible for the disappointing initial results of cancer vaccination trials for NSCLC [8,9,10].

Vaccines are often categorised by their type of antigen. In the group of cellular vaccines, ‘autologous cell vaccines’ have the advantage to elicit an immune response to a large variety of antigens expressed by the patient’s tumour, but their production and standardisation is complex and a major problem for large-scale development [16], as illustrated by the experience with the granulocyte–macrophage colony-stimulating factor-enhanced
autologous vaccine (G-VAX®, Cell Genesys, San Francisco, CA) [17, 18]. One compound based on ‘allogeneic cells’ is in phase III development in NSCLC (belagenpumatucel, Lucanix®, NovaRx, San Diego, CA). This approach is based on mixtures of NSCLC cell lines and overcomes some of the logistical concerns, but the relation to the clinically relevant tumour remains uncertain. ‘DC vaccines’ consist of APCs loaded with tumour antigen(s), their production process equally being technologically challenging. In the group of compound directed vaccines, the ‘peptide vaccines’ are easy to manufacture but have the disadvantage of targeting only one or a few epitopes and thus poorer immunogenicity [16]. This shortcoming can be circumvented by using efficient delivery systems and/or immunoadjuvants such as in the L-BLP25 vaccine (Stimuvax®, Merck, Darmstadt, Germany) [19]. ‘Recombinant protein-based’ vaccines can elicit an immune response against multiple epitopes, but here as well, the use of immunoadjuvants to facilitate uptake of the protein by DCs is required, as in the Melanoma AntiGEn A3 (MAGE-A3) or the epidermal growth factor (EGF)-directed vaccines [20]. Finally, ‘viral vaccines’ are based on viruses. One such vaccine consists of a suspension of attenuated Ankara virus, a vaccinia virus, genetically modified to express antigens and co-stimulatory cytokines. Their effect may be limited by neutralising immune responses [16].

Table 1. Overview of cancer vaccination in different NSCLC treatment settings

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<tr>
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BSC, best supportive care; CT, chemotherapy; CTRT, chemoradiotherapy; DFI, disease-free interval; DFS, disease-free survival; HR, hazard ratios; IL, interleukin; MAGE-A3, Melanoma AntiGEn A3; MUC1, mucinous glycoprotein-1; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; TGF, transforming growth factor.

Different vaccines are in late-stage development in different NSCLC treatment settings (Table 1). For early-stage NSCLC, the MAGE-A3 vaccine is in phase III testing; for locally advanced stage, there is the L-BLP25 vaccine; and for advanced stages, several compounds are in randomised controlled trials: belagenpumatucel-L, the EGF vaccine, and the TG4010 vaccine (Figure 2). It is often presumed that cancer immunotherapy is most likely to be successful in patients with low tumour burden, but the recent phase III experience with ipilimumab in metastatic melanoma [14] and sipuleucel-T, an autologous active cellular immunotherapy, in metastatic prostate cancer [21] has challenged this view. The results of the ongoing phase III studies in NSCLC will hopefully answer which strategy will be the most rewarding.

**early-stage NSCLC: surgical multi-modality context**

Early-stage NSCLC encompasses stages I to (potentially resectable) IIIA NSCLC. The current standard treatment is mainly surgical resection. However, despite complete resection of the tumour, patients are still at high risk of relapse. The 5-year survival of patients with resected stage I A NSCLC is 73% and drops to only 24% in stage IIIA NSCLC. [22]. Adjuvant cisplatin-based chemotherapy reduced the risk of relapse and...
increased 5-year survival by ~5% in a meta-analysis [23] and has become the standard of care for stages II and IIIA and under debate for some patients with stage IB. However, many patients will not receive chemotheraphy, either because of patient’s refusal or because of associated co-morbidities [24]. Moreover, compliance with cisplatin-based regimens in the clinical trials was only ~50% to 74%, illustrating the need for better tolerated therapies. In the setting of early-stage NSCLC, the aim of postoperative vaccination is to eliminate as much as possible cancer cells remaining after radical treatment, in order to delay or even avoid relapse and improve cure rates.

The normal function of MAGE-A3 is unknown, but its presence on tumour cells has been associated with worse prognosis [25]. The MAGE-A3 antigen is expressed in a variety of tumour cells, but not in normal tissues (except for the testis, which does not compromise true tumour specificity, as the antigen is not presented there in the absence of MHC molecules). In NSCLC, expression can be demonstrated in 35% of early-stage tumours [26]. The ‘MAGE-A3 vaccine’ is an example of a recombinant protein antigen-based vaccine and is the only one in large-scale development in the postoperative setting. The current vaccine is composed of a recombinant fusion protein (MAGE-A3 and protein D of Haemophilus influenzae) in combination with an immune response-enhancing adjuvant (AS02B in the phase II study and AS15 in phase III) [20].

In a proof of concept phase II study, 182 patients with completely resected, pathological stage IB/II had fresh tumour tissue tested for MAGE-A3 expression by reverse transcriptase PCR. MAGE-A3-positive patients were randomly (2 : 1) assigned to either the MAGE-A3 vaccine (300 µg i.m., 5 administrations q3 weeks followed by 8 administrations q3 months) or the same schedule of placebo. No adjuvant chemotherapy was given, as this therapy was not established in the absence of MHC molecules. In NSCLC, expression can be demonstrated in 35% of early-stage tumours [26]. The ‘MAGE-A3 vaccine’ is an example of a recombinant protein antigen-based vaccine and is the only one in large-scale development in the postoperative setting. The current vaccine is composed of a recombinant fusion protein (MAGE-A3 and protein D of Haemophilus influenzae) in combination with an immune response-enhancing adjuvant (AS02B in the phase II study and AS15 in phase III) [20].

Currently, a double-blind phase III trial (MAGRIT, NCT00480025) is recruiting patients with completely resected stage IB/II/III MAGE-A3-positive NSCLC. It is expected that at least 10 000 resected patients will need to be screened in order to randomise 2270 patients, either after surgery or after surgery plus adjuvant chemotherapy. The primary end point for this trial is DFS. While OS has been the historical standard end point, DFS is an attractive surrogate end point, as it is more rapidly available and not blurred by the effect of increasingly effective therapies at the time of relapse. An individual patient data meta-analysis on 7626 patients from 25 randomised trials recently showed that there is a very strong correlation between DFS and OS and thus good evidence that DFS is a valid end point as well [29].

**unresectable, locally advanced stage III NSCLC: non-surgical multi-modality context**

Stage III NSCLC groups patients with locally advanced tumours without distant metastasis. While surgery may offer benefits for some stage IIIA patients [30], most of the fit stage III patients will have a multi-modality approach, combining chemotherapy and radiotherapy. In comparison with radiotherapy alone, concurrent chemoradiotherapy leads to an increase in 2- and 5-year survival rates from 21.4% to 25.4% and from 6.0% to 8.2%, respectively [31]. New strategies adding additional treatments to keep patients in remission and perhaps further improve survival are highly needed, as large trials have failed to achieve this until now [32, 33].

Mucinous glycoprotein-1 (MUC1) is a highly glycosylated transmembrane protein that is present in normal tissue but usually only at the apical surface of the epithelial cell [34]. Its exact function remains unclear, but MUC1 might be involved in promoting cell growth and survival [35]. In cancer cells, MUC1 loses its polarity of expression, is often overexpressed, and is under- or aberrantly glycosylated, which results in unmasking of its peptide epitopes, thus revealing a potential target for immunotherapy [19].

The ‘L-BLP25 vaccine’ (Stimuvax®) is a peptide antigen-based vaccine that targets this exposed core peptide of the MUC1-associated antigen. The L-BLP25 vaccine contains the BLP25 lipopeptide (which consists of 25 aminoacids) and a liposomal delivery system (consisting of cholesterol, dimyristoyl phosphatidylglycerol, and dipalmitoyl.
phosphatidylcholine), which facilitates uptake by APCs, and monophosphoryl lipid A, which is added to enhance immune stimulation [36].

In a phase II randomised trial, 171 patients with stage IIB/IV NSCLC, who had disease control (response or stable disease) after first-line therapy (consisting of either chemotherapy alone or chemotherapy and radiotherapy), were randomised to receive L-BLP25 with best supportive care (BSC) or BSC alone. Patients in the L-BLP25-arm received i.v. cyclophosphamide (300 mg/m²) 3 days before immunotherapy, followed by 8 weekly s.c. injections with the L-BLP25 vaccine (1000 µg), and subsequently L-BLP25 q6 weeks at the investigator’s discretion. The primary end point was OS. The median OS time was 17.4 versus 13 months in favour of the L-BLP25 group (adjusted HR 0.739; 95% CI 0.509–1.073; \( P = 0.112 \)) [37]. In a post-hoc analysis by stage, patients with stage IIB malignant effusion or stage IV disease did not show any survival benefit, but for patients with non-pleural stage IIB, the median OS was ‘not reached’ versus 13.3 months (adjusted HR 0.524; 95% CI 0.261–1.052; \( P = 0.069 \)). The L-BLP25 vaccine was associated with a good safety profile with mostly grade I flu-like symptoms and injection site reactions. Long-term analyses confirmed both findings: in the updated survival analysis, median and 3-year OS were 30.6 versus 13.3 months and 49% versus 27% (HR 0.548, 95% CI 0.301–0.999, \( P = 0.070 \)) [38]; long-term use of the vaccine (follow-up up to 7.7 years) did not reveal any major or additional safety issues [39].

On the basis of these results, a large phase III trial started in December 2006. Recruitment was completed early June 2011. This START-trial (NCT00409188) randomised 1464 patients with unresectable stage III NSCLC who had stable disease or an objective response after previous chemoradiotherapy. Patients (2 : 1) received L-BLP25 plus BSC or placebo plus BSC. The primary end point was OS. Simultaneously, a second phase III trial with similar study design and end points is ongoing in Asia (INSPIRE, NCT01015443).

advanced stage NSCLC: metastatic context

The median OS of untreated patients with advanced NSCLC is ~4 to 6 months, with <10% of patients alive at 1-year follow-up. Historically, these patients were treated with a platinum compound (cisplatin or carboplatin) in combination with a third generation compound [gemcitabine, vinorelbine, paclitaxel, docetaxel, pemetrexed]. This ‘any platinum doublet fits all’ strategy resulted in a median OS of only 8–10 months and a 1-year survival rate of 33% [40]. Targeted therapies such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors have proven to be true assets in the treatment of advanced NSCLC harbouring an activating EGFR mutation [41], and the same is expected for crizotinib in tumours with the EML4-ALK oncogene fusion gene [42]. Until lung cancer genetics and more targeted therapies become readily available in clinical practice, many patients will still have to rely on cytotoxic chemotherapy for the treatment of their NSCLC. Therefore, new treatment approaches are needed and immunotherapy may fill a gap there. Different vaccines are currently being evaluated in phase III trials in the setting of metastatic disease.

belagenpumatucel-L (Lucanix®)

This is an allogeneic cell vaccine. It consists of four different NSCLC lines (two adenocarcinoma, one squamous cell carcinoma, and one large cell carcinoma), thus representing a large array of antigens. The immunoadjuvant principle is based on downregulation of TGF-β2 (see above) by transfecting the cells with a TGF-β2 antisense gene [43].

The efficacy and safety of belagenpumatucel-L was investigated in 75 NSCLC patients (14 with stage II/IIIA and 61 with low-volume—i.e. tumour volume <125 ml—stage III/IV). In a phase II dose-range study, 12.5, 25, or 50 × 10⁶ cells per injection on a monthly or every other month schedule for up to 16 injections were administered. In the subgroup of 61 patients with advanced (stages IIB and IV) disease, a partial response rate of 15% was achieved. The study did not have a control group with chemotherapy alone, but advanced stage patients who received ≥25 × 10⁶ cells per injection (high-dose group) showed a better OS than those who received 12.5 × 10⁶ cells per injection (low-dose group) with an estimated 2-year survival of 47% in the higher dose group versus 18% in the lower dose group [43]. In subgroup analysis, patients in whom both a cellular and a humoral immune response to the vaccine could be demonstrated had improved OS compared with patients classified as immune response negative (median OS 32.5 versus 11.6 months, \( P = 0.011 \)) [44]. This vaccine is currently further being evaluated for efficacy and safety in the STOP trial (NCT00676507), a randomised phase III trial comparing intradermal belagenpumatucel-L (25 × 10⁶ cells in 0.4 ml) versus placebo following platinum-based chemotherapy—once monthly for 18 months and then once at 21 and 24 months if no disease progression or unacceptable toxicity—in ~700 patients with stage IIIA (T3N2 only), IIB, or IV NSCLC. The primary end point is OS.

EGF vaccine (CimaVax®, Center for Genetic Engineering and Biotechnology, Havana, Cuba)

Another potential immunotherapy target is the EGFR pathway, involved in cell proliferation, apoptosis, angiogenesis, and metastasis. Different inhibitors of the EGFR signalling pathway, including mAbs and small-molecule tyrosine kinase inhibitors, are already being used in clinical practice. The EGF vaccine was developed in Cuba with recombinant human EGF coupled to a carrier protein (P64K Neustria meningitides protein) and with an immunoadjuvant (aluminium hydroxide or Contained ISA51) [45].

In a phase II study, 80 patients with stage IIB or IV were randomised after completion of first-line chemotherapy to receive BSC alone or with the EGF vaccine [46]. After priming with cyclophosphamide (200 mg/m²), a dose containing 50 µg equivalents of EGF was administered on days 1, 7, 14, and 28 (a monthly or every other month schedule for up to 16 injections). Immune response seemed to predict benefit from treatment: patients with a good antibody response (defined by anti-EGF antibody titres ≥1 : 4000 and at least four times their pre-immunisation values) had a median OS of 11.7 versus 3.6 months for the others (\( P = 0.002 \)) [46].
The EGF vaccine is already licensed in Cuba for use in stage IIIB/IV NSCLC. A phase II/III trial is ongoing in Malaysia to assess the safety, immunogenicity, and efficacy of the EGF vaccine in patients with stage IIIB/IV NSCLC after receiving conventional first-line chemotherapy (NCT00516685). The primary end point is OS.

**TG4010 vaccine**

This compound also targets the MUC1 antigen. The vaccine consists of a suspension of attenuated Ankara virus, a vaccinia virus, genetically modified to express not only MUC1 but also IL-2 [47]. It has been demonstrated that addition of exogenous IL-2 is a strong immunoadjuvant as it is able to reverse the suppression of T-cell response caused by the cancer-associated MUC1 mucin [48]. In a multicentre, open-label phase II randomised study, 148 untreated patients with MUC1+ stage IIIB/IV NSCLC were randomised to receive up to six cycles of cisplatin–gemcitabine with or without TG4010. The vaccine was given s.c. weekly for 6 weeks and then q3 weeks until disease progression. The primary end point—a PFS rate at 6 months of >40% in the experimental arm—was reached (44% versus 35%, \( P = 0.13 \)). A higher response rate was seen in the vaccinated group (43% versus 27%, \( P = 0.03 \)). In a subgroup analysis in patients with a normal level of activated natural killer cells, PFS at 6 months was 58% versus 38%, \( P = 0.04 \), with a significant OS difference in this subgroup (18 versus 11.3 months, \( P = 0.020 \)) [49]. A phase IIb/III, randomised, double-blind, placebo-controlled trial (NCT01383148) aiming to enrol 1000 MUC1-expressing stage IV patients with normal levels of activated natural killer cells is expected to start end of 2011. Patients will have four to six cycles of platinum doublet chemotherapy (bevacizumab allowed if prescribed) and TG4010 or placebo until progression or discontinuation due to any reason in the same schedule as described above. The primary end point is OS.

**conclusion**

In recent years, new insights in the interaction between tumours and the immune system have led to the development of immunotherapy as a fundamentally new concept for the treatment of NSCLC. Since the disappointing introduction of the first therapeutic cancer vaccines, the better identification of antigenic targets, the addition of immunoadjuvants, and the production of more efficient delivery systems have resulted in more sophisticated vaccines, able to elicit a potent immune response. Recent positive phase III data in indications other than NSCLC have helped to establish the proof of principle for cancer vaccination. In NSCLC, different vaccines have shown promising signals, with demonstration of immune responses following treatment and encouraging phase II efficacy and safety data. The results of ongoing phase III investigations are eagerly awaited, hopefully confirming the promising results and proving the value of cancer vaccination as a new mode of treatment of different stages of NSCLC.

**disclosure**

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