NON-SMALL CELL LUNG CANCER: PRESENT TREATMENT AND UPCOMING IMPROVEMENTS

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ABSTRACT

Lung cancer it has been the leading cause of the cancer – related death
worldwide, lung cancer has a poor prognosis; most of the people
diagnosed with lung cancer die within one year of the diagnosed and 5-
year survival is less than 18% non-small cell lung cancer [NSCLC]
explanation for the majority of all lung cancer cases .most of cases for
developing NSCLC have been known, with cigarette smoking being a
main factor along with other environmental and genetic risk
factor.Developing on the staging of lung cancer, patients are suitable
for certain treatment going from surgery to radiation to chemotherapy
as well as targeting therapy. with improvement of genetic and
biomarkers testing ,particular mutation have been known to better
target treatment for individual patient .this review article gives the
present treatment including surgery ,chemotherapy ,radiotherapy and
immunotherapy as well as how biomarker sting has assisted improve survival in patient with
non-small cell lung cancer[NSCLC]

KEYWORDS: chemotherapy, immunotherapy, non-small cell lung cancer

INTRODUCTION

Lung cancer is among the most deadly cancers for both men and women.[1] Its death rate
exceeds that of the three most common cancers [colon, breast, and pancreatic] joined.[2].Over
half of patients diagnosed with lung cancer die within one year of diagnosis and the 5-year
survival is around 17.8%.[3].There are two leading subtypes of lung cancer, small cell lung
carcinoma and non-small-cell lung carcinoma [NSCLC], accounting for 15% and 85% of all

lung cancer, correspondingly.[4] NSCLC is further classified into three types: squamous-cell carcinoma, adenocarcinoma, and large-cell carcinoma Squamous-cell carcinoma comprises 25–30% of all lung cancer cases. It arises from early forms of squamous cells in the airway epithelial cells in the bronchial tubes in the center of the lungs. This subtype of NSCLC is strongly associated with cigarette smoking.[5].The greatest common type of lung cancer is adenocarcinoma; it contains around 40% of all lung cancer. It arises from small airway epithelial, type II alveolar cells, which secrete mucus and other substances.[6] Adenocarcinoma is the most common type of lung cancer in smokers and nonsmokers in men and women regardless of their age.[7] It tends to occur in the periphery of the lung.[8] which might be due to the addition of filters in cigarettes preventing large particles from entering the lungs. This results in deeper inhalation of cigarette smoke, leading to peripheral lesions .[9] Associated to other types of lung cancer, adenocarcinoma tends to produces lower and has a greater chance of being found before it has spread outside of the lungs. Large cell [undifferentiated] carcinoma accounts for5–10% of lung cancers. This type of carcinoma shows no indication of squamous or glandular maturation and as a result is often diagnosed by default through barring of other possibilities. Great cell carcinoma often begins in the vital part of the lungs, sometimes into nearby lymph nodes and into the chest wall as well as distant organs.[10].Large cell carcinoma tumors are strongly linked with smoking.[11].

RISK FACTORS

Smoking one of the important risk factor for lung cancer.[2]. When cigarettes became the major tobacco product manufactured in the 1900s, lung cancer became more common. Rises in the number of years or the number of packs smoked per day increases the grade of risk for lung cancer.[12].Smoking causes at least 80% of lung cancer deaths. A comparative risk of developing lung cancer from passive smoking was found to be 1.14 to 5.20 in people who had never smoked but lived with a smoker based on a meta-analysis and comprehensive review.[13]. According to the U.S. Surgeon General, living with a smoker can increase nonsmoker's chance of evolving lung cancer by about20–30%.[14].Radon, a naturally occurring carcinogen, is among the risk factors connected with lung cancer, and approximately21,000 lung cancer deaths in the United States have been linked to radon exposure.[15] Although radon was initially linked with mine workers, there has been growing concern attributed to indoor radon exposure from natural uranium deposits that are commonly found in basements. A collection of case-controlled studies from North American, Europe, and China has demonstrated increased incidence rates of lung cancer linked to residential

radon exposure at levels of 2.7 picocuries per liter [pCi/L].[16-18].Lung cancer is considered one of the most common cancers caused by occupational exposures. The use of asbestos in industry or manufacturing has been linked to increased incidence of mesothelioma and lung cancer.[19,20].An association between asbestos fiber sizes as a strong predictor of lung cancer mortality has been found.[21].Consequently, the U.S. government has taken steps to reduce asbestos use in commercial and industrial projects. Other occupational exposures linked to lung cancer contain the use of arsenic and arsenic compounds [antifungal, outdoor wood preservatives, insecticides, herbicides, etc.]exposure to beryllium and beryllium oxide [X-ray and radiation technology, etc.], inhaled chemicals including cadmium, silica, vinyl chloride, nickel compounds, chromium compounds, coal products, mustard gas, and chloromethyl esters and diesel exhaust.[22, 23].In large cities and other areas with traffic crowding, long-term and accumulated exposure to air pollution, including emissions composed of polycyclic aromatic hydrocarbons, is recognized as a lung cancer risk factor.[24]. Air pollution has-been connected with an 8% increased risk of all-cause lung cancer mortality.[25].Personal or family history of lung cancer helps as a risk factor for a person to grow lung cancer.[26]. There are certain genes and chromosomes that have been related to an increased risk of lung cancer. Carriers of TP53 germ line sequence differences who also smoke are more than 3 times more likely to develop lung cancer than nonsmokers.[27].There are also reports of a marker on chromosome 15associated with lung cancer, which was discovered in three independent genetic studies.[28-30].The marker contains three genes for subunits of the nicotine acetylcholine receptor. Cell change can happen when nicotine latches onto this protein, positioned on the cell surface. Based on results from these three independent studies, people with one copy of the marker have a 30% increased risk of developing lung cancer, while people with two copies have an increased risk of 70–80%.

PRESENT TREATMENT SELECTIONS

Surgery

Patients who have phase I, II, and IIIA NSCLC usually have surgery to eliminate the tumor if the tumor is found to be resect able and the patient is capable to tolerate surgery. Surgeons may eliminate a lobe or piece of the lung having the tumor. To determine if the tumor is resectable, imaging studies and biopsies are finished as well as an evaluation of patient factors to determine operability. Presently, many surgeons utilize video-assisted thoracoscopic surgery [VATS], where a small incision is made in the chest and a thorascope is inserted. A

lobe cans be removed via the scope through this small incision so that a higher incision does not have to be made.[31]

ADJUVANT

Certain patients who have undergone a resection surgery may benefit from adjuvant therapy in dipping the risk of lung cancer relapse. Adjuvant therapy may contain radiation, chemotherapy, and targeted therapy. Patients with phase IA, IIB, and IIIA NSCLC usually obtain chemotherapy after surgery to kill any remaining cancer cells in order to prolong survival.[32]

Chemotherapy

About 40% of freshly diagnosed lung cancers patients are stage IV. The goal for treating these patients is to progress survival and decrease disease-related adverse events. For stage IV NSCLC, cytotoxic combination chemotherapy is the first-line therapy, which might be influenced by histology, age vs. comorbidity, and performance status [PS].[33] The American Society of Clinical Oncology states that treatment for a patient with a PS of 0 or 1 Isa regimen of a platinum [cisplatin or carboplatin] pluspaclitaxel, gemcitabine, docetaxel, vinorelbine, irinotecan, or pemetrexed.[34] Results from four large multicenter randomized clinical trials studying the above agents with either platinum or carboplatin have yielded similar results. From these studies, results have shown that no single regimen demonstrated a significant superiority over any other combination. Median overall survival for patients in these studies was approximately 8–10 months.[35-38]. The specific combination depends on types and frequencies of toxic effects and should be obvious on an individual basis. However, adenocarcinoma patients may benefit from pemetrexed. Cisplatin is the slightly more active platinum; however it has been linked with more sideeffects. For patients with a PS of 2, indication suggests that they may need only one drug, which is usually not platinum.[39] For chemotherapy treatment, serious adverse events should prompt a change in agents. Therapy should also be stopped if the cancer produces or if, after four treatment cycles, the disease is steady but the treatment is not shrinking the tumors.[40,41]. Patients with a PS of 3 do not typically benefit from getting cytotoxic chemotherapy because the risk of adverse events could worsen their excellence of life significantly. For these patients basic supportive care is generally suggested.

Radiotherapy

Radiotherapy uses high-energy beams to damage DNA within cancer cells, thereby terminating them. This therapy can benefit control or remove tumors at specific sites in the body. Patients with NSCLC that is localized to the chest and who are not candidates for surgical resection may help from radiotherapy. Radiotherapy also can be part of palliative care to increase quality of life in NSCLC patients who do not respond to surgery or chemotherapy.[42].A technique called stereotactic body radiation therapy [SBRT] is used for early-stage NSCLC patients who have a single small nodule in the lung without any metastases to nearby lymph nodes. This technique uses an advanced coordinate system to surely locate the tumor and ensure precise placement of the tracking device. This permits delivery of concentrated and highly focused radiation treatment. In a meta-analysis comparing the effectiveness of radiotherapy with photons, protons, and carbon-ions for NSCLC, it was found that SBRT offered greater 2-yearoverall survival rates, lower costs, and better patient convenience.[43]. In a prospective phase II study, 50-monthresults of 70 medically inoperable patients getting SBRTshowed that getting SBRT resulted in high rates of local control in medically inoperable patients with Stage 1NSCLC.[44] In a phase III multicenter study of patients with early stage but medically inoperable NSCLC, toxicity and efficacy of SBRT was studied. Of the 55 patients evaluated, it was found that patients who received SBRT had a survival rate of 55.8% at three years along with moderate treatment-related morbidity.[45] As a result of these studies and several others, SBRT has been found to offer local control and outcomes approaching surgical resection with lower rates of treatment-related morbidity.[46, 47].

Biomarker testing

Personalized medicine by targeting suitable molecular targets in tumors has facilitated improves survival in patients with NSCLC [48]. There are targeted agents that have been effective against epidermal growth factor receptor [EGFR] mutations and anaplastic lymphoma kinase [ALK] relocations. Through genomic testing, other molecular changes have been found including gene rearrangements of ROS1 and RET amplification of MET and activating mutations in BRAF, HER2 and KRAS genes, which might be potential targets for upcoming therapies.

Epidermal growth factor receptor (EGFR) gene

EGFR is a cell-surface tyrosine kinase receptor that can activate pathways connected with cell growth and proliferation when activated. In cancers, mutations of EGFR produce uncontrolled cell division through constant activation. EGFR gene mutations are present in 10–15%of lung cancer adenocarcinomas patients who are of European and Asian descent, in those who have never smoked, and female.[49-51]. While these characteristics are predominant, mutation testing is integral to finding those patients who would benefit from targeted tyrosine kinase inhibitor therapy. Exons 18–21 are where mutations in EGFR commonly occur, which confers sensitivity to EGFR tyrosine kinase inhibitors; these exons encode a portion of the EGFR kinase domain. Around 90% of these mutations are exon 19 deletions and L858R point mutation on exon 21 and are correlated with a response rate of 70%in patients receiving erlotinib or gefitinib treatment.[52]

KRAS

KRAS is a common mutated oncogene connected with NSCLC due to missense mutations that substitute an amino acid at position, 12, 13 or 61. Single amino acid mutations at residues G12 and G13 are predominantly known. KRAS mutations are recognized more frequently in adenocarcinomas, Caucasians, and individuals with a smoking history.[53] Approximately 10–25% of patients with adenocarcinoma have KRAS mutation-associated tumors.[54] In terms of overlapping with other oncogenic mutations, KRAS has been predominantly found in tumor types that are wild type for EGFR and ALK, meaning these mutations are a new molecular subset of NSCLC. Emerging data recommends that there could be a possible prognostic value of KRAS mutations but a limited role as predictor for EGFR tyrosine kinase inhibitors or cytotoxic chemotherapy.[48,52]. One study has suggested that it is possible to directly target a KRAS mutational subset with small-molecule inhibitors directed towards the commonG12C lung cancer mutation, a common mutation in smokers vs. non-smokers. These possible new agents rely on mutant cysteine for binding and do not affect the wild-typeKRAS protein, thereby showing selectivity for a precise subtype.[55]

Anaplastic lymphoma kinase (ALK)

Almost 3–7% of all lung tumors have ALK mutations.[56-58] where these mutations are usually seen in patients who are of a younger age. In a study by Koh et al., patients with ALK mutations had a median age of 49 compared to a median age of 61 in patients who were ALK negative [P<0.001; n=221].[59]. ALK mutations are also more common in adenocarcinoma

patients with acinar histology or signet ring cells or those who have never smoked.[60, 61]. Rearrangement in EML-4-ALK is the most common ALK rearrangement seen in NSCLC patients. These rearrangements arise on chromosome2p23 due to the fusion between the 5' and of the EML-4gene and the 3' end of the ALK gene, of which there are at least nine different fusion variants. EML-4 mutations are common in adenocarcinomas of patients who had never smoked or had been light smokers whose tumors lack both EGFR and KRAS mutations.[56,61]. ALK mutations are non-overlapping with other oncogenic mutations related with NSCLC such as EGFR or RAS.[61,62] Other ALK mutations not involving EML-4 have been found, includingKIF5B-ALK and TFG-ALK. In terms of treatment, patients with EML4-ALK fusions or ALK rearrangements do not benefit from EGFR-specific tyrosine kinase inhibitor therapy[63].Currently there is an FDA-approved agent, crizotinib [Xalkori®, Pfizer], that targets constitutively activated receptor tyrosine kinases that result from EML4-ALK and other ALK fusions. In a single arm study of ALK-positive metastatic NSCLC.[64] patients exhibited objective response rates of 50–61%. In a trial with previously untreated advanced non-squamous ALK-positive NSCLC, patients were randomized to receive crizotinib 250 mg by mouth twice a day [n=172] or intravenous chemotherapy [pemetrexed 500 mg/m2 plus either cisplatin 75 mg/m2 or carboplatin target area under the curve 5–6 mg/mL/min [PPC group]; all administered intravenously every three weeks for ≤6 cycles, n=171]. The primary endpoint of the study was progression-free survival while the secondary endpoints included overall response rate, overall survival, safety, and patient-reported outcomes. They found that crizotinib prolonged progression-free survival 10.9 vs.7 months in patients receiving PPC. The overall response rate was also higher in patients receiving crizotinib at74% vs. 45% in patients receiving PPC. Overall crizotinib showed important improvements in progression-free survival and overall response rate compared with standard chemotherapy and its safety profile was acceptable.[64].This pivotal trial established crizotinib as the standard of care for patients with previously untreated, advanced ALK positive non-squamous NSCLC.

BRAF

BRAF is a proto-oncogene, which is a regulated signal transduction serine/threonine protein kinase that is able to promote cell proliferation and survival [65]. BRAF somatic mutations have been found in 1–4% of all NSCLC, most usually in patients with adenocarcinomas [54,66-70].These mutations are more commonly linked with former/current smokers.[69,70]. The kinase domain locations of BRAF mutations in lung cancer patients vary from BRAF

mutations in breast cancer patients. In a study of 697patients with lung adenocarcinoma, BRAF mutations were.

Table 1 some result immunotherapy trial non-small cell lung cancer

Immunotherapy type	Agent[s]	phase	Result	Ref
Anti CTLA-4	lipillimumab	III	Ipilimumab with or without gp100 improved survival vs. gp100 alone	76
	Ipilimumab+ Paclitaxel + Carboplatin	II	Given as a phased regimen improved immune-related progression-free survival and progression-free survival	77
PD-1	Nivolumab	I	Patients with previously treated advanced NSCLC treated with nivolumab showed a sustained overall survival benefit across different histology	78'79
PD-1	Nivolumab vs docetaxel	III	Nivolumab demonstrated superior overall survival when compared to Docetaxel	80
PD-L1	MK-3475		MK-3475 is generally well-tolerated and can provide robust antitumor activity for patients that express PD-L1	81

Anti CTLA-4 T lymphocyte-associated antigen; PD-I, programmed cell death 1

Present in 18 [3%], of which the BRAF mutations recognized were V600E [50%], G469A [39%] and D594G [11%].[69].A great majority of BRAF mutations have been found to be non-overlapping with other oncogenic mutations in NSCLC [EGFR mutations, ALK rearrangements, etc.].

Role of immunotherapy in non-small cell lung cancer

Immunotherapy is one of a breakthrough treatment in oncology that uses the body's own natural defense system to fight off cancer. Some cancer cells share characteristics with healthy cells and thus the immune system cannot differentiate between the body's normal and abnormal [cancer] cells.[71].It is thought that immunotherapy works by enhancing the immune system so that it can target cancer cells and stop or slow the growth of cancer cells, by stopping cancer cells from spreading to other parts of the body, or by helping the immune system increase its effectiveness.[72]. Data has shown that improved survival is associated with a strong antitumor immune response. Higher numbers of CD4+ T cells, CD8+ T cells, natural killer cells, and/or dendritic cells are associated with better patient survival.[73-75].New strategies in immunotherapy are targeting immune-modulating mechanisms that help tumor cells defend themselves against the immune system [Table 1].This approach targets immune

checkpoint pathways, which includes the blockade of the inhibitory receptors cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4]and programmed cell death-1 [PD-1] and its ligand, PDL1.These immune checkpoints are used by the immune system to maintain self-tolerance and regulate the immune response in the body to protect tissues from damage as the immune system launches a response to a pathogen.[82].Immune checkpoint pathways can be deregulated by tumor resistance mechanisms.

Cytotoxic T-lymphocyte-associated antigen 4 [anti- CTLA-4] therapy

CTLA-4 has an significant role in down-regulating Tcell activation, proliferation, and effector functions.[83].Ipilimumab therapy in patients previously treated for metastatic melanoma confirmed improved overall survival.[84]. Key analyses from a phase III trial showed that in the ipilimumab-alone group, 1-year survival was assessed to be 45.6% vs. 21.6–38% in patient's getting the other treatment regimens in the study. After two years, approximately 24% of the patients who received ipilimumab were still alive.[76].Ipilimumab in combination with paclitaxel and carboplatin in two different treatment schedules [phased or concurrent] was evaluated in chemotherapy-naïve patients who had stage IIIb or IV NSCLC. This was a phase II trial in which the primary endpoint was an improvement of the immune-related progression-free survival.[77]. Patients in the concurrent treatment arm received ipilimumab concurrently for four doses followed by placebo, while the patients in the phase arm received two doses of placebo and then four doses of ipilimumab. Following six cycles of the combination, patients received a maintenance regimen of placebo or ipilimumab every 12 weeks or until disease progression. When comparing the phased schedule versus chemotherapy alone, immune-related overall response rate was nearly doubled [32% vs. 18%, respectively]. Progression free survival progresses in patients with squamous cell histology has prompted a larger trial using the same schedule in patients with squamous cell carcinoma.

Programmed cell death-1 [PD-1] and PD-L1

The PD-1 immune checkpoint pathway is an extra target for NSCLC therapy. It has a role in preventing T cell activation through down-regulation of the immune system, which promote self-tolerance and reduces autoimmunity. Ultimately, the blocking of this pathway augments the Tcell response in the body.[85,86]. There have been some promising results in early clinical trials with two agents, nivolumab and MK-3475, discussed next. Nivolumab was recently approved by the FDA in October, 2015, based on the Checkmate 057 trial that showed

enhancement in overall survival in an open-label and randomized multicenter trial comparing nivolumab todocetaxel in metastatic non-squamous NSCLC patients.[78,79]. Checkmate 017 was an open-label, international and randomized trial comparing nivolumab to docetaxel in previously treated patients with advanced, squamous cellNSCLC, and it was stopped early by Bristol-Myers Squibb after meeting its end point.[80]. Overall survival and an objective response rate and progression-free survival were assessed in the trial, which randomized 272 patients with advanced or metastatic squamous cell NSCLC to receive nivolumab or docetaxel. According to the study's Data Monitoring Committee, nivolumab demonstrated superior overall survival when compared to docetaxel.MK-3475 is a humanized monoclonal antibody that targets the ligand of PD-1, PD-L1, thereby removing the inhibition of T cell activation against tumor cells. One study looked at 84 NSCLC patients with no prior systemic therapy for metastatic disease; these patents were then tested to see if the tumors in their tissue expressed PDL1.[81] Of these, 57 patients had tumors that expressedPD-L1, however only 45 were eligible to be randomized to receive 2 mg/kg of MK-3475 every three weeks [n=6], 10 mg/kg every three weeks [n=23], or 10 mg/kg every two weeks [n=16]. Overall response rate was 36% across all groups [67% in the 2 mg/kg every three weeks group, 27% in the 10 mg/kg every three weeks group, and 35%in the 10 mg/kg every two weeks group]. Common side effects included fatigue, pruritus, diarrhea, and dyspnea and dermatitis acneiform. Data from this study suggests that MK-3475 is generally well tolerated and effective in patients with locally advanced or metastatic NSCLC that expresses PD-L1.

Immunotherapy through vaccine development

The objective of vaccine therapy in NSCLC is to shift the immune balance in favor of activation so that the host may launch a response to tumor-associated antigens.[87, 88]. Presently there are two developing strategies to use vaccines in the treatment of NSCLC: tumor vaccines and antigen-specific immunotherapy [Table 2]. Tumor [whole-cell] vaccines are developed from autologous or allogeneic tumor cells. These vaccines work by exposing the host's immune system to several tumor-associated antigens [99]. Antigen-specific immunotherapy incorporates specific antitumor immunity against antigens expressed on tumor cells. Since these vaccines target a specific antigen, they may not be able to be used in all patients. Presently there are some ongoing phase III trials involving potential new vaccine therapies in NSCLC [Table 2].

Tumor cell vaccines

Belagenpumatucel-L [Lucanix®, NovaRx Corp.] is anallogenic tumor cell vaccine using genetically modified whole tumor cells. It is composed of 4 irradiated NSCLClines gene-modified with transforming-growth factor[TGF]-β2, of which 2 are adenocarcinoma lines, 1 is a squamous line, and one is a large-cell carcinoma line [H460,H520, SKLU-1, and RH2, respectively] [100]. Higher levels of [TGF]-β2 are associated with suppression of the immune system, which leads to neutralization of natural killers cells and suppression of dendritic cells [101]. Another role of belagenpumatucel-L is that it has immune-stimulating effects through activation of a specific T cell response against NSCLC cells. The plasmid [TGF]-β2 transgene portion of the vaccine may suppress tumor production through its expressed antisense RNA.[102].Belagenpumatucel-L was evaluated [phase II clinical trial] in 75 patients with NSCLC stages II-IV and was well tolerated with positive responses in patients who showed raised antibody levels.[89]. In a phase III trial of belagenpumatucel-L, patients without progression after completion of frontline chemotherapy [phaseIIIA, n=42; phase IIIB/IV, n=490] were randomized 1:1[belagenpumatucel-L or placebo] between 4 and 17.4 weeks from the end of frontline chemotherapy and were treated until disease progression or withdrawal.[90]. The study evaluated the utility of belagenpumatucel-L in improving overall survival. Secondary endpoints of the study involved progression-free survival, response rate, and safety. Of the enrolled 532 patients] 270 vaccine and 262 placebo [, 57%had adenocarcinoma and 27% had squamous cell carcinoma. This study did not achieve its predefined primary endpoint; median overall survival in the vaccine group was 20.3 vs.17.8 months in the placebo group [hazard ratio [HR] 0.94; P=0.594]. A predefined COX regression helped recognize prognostic factors for improved outcome and showed a important and clinically meaningful greater overall survival in the vaccine group over placebo. The overall survival was improved by 7.3 months in the vaccine group for patients who were randomized within 12 weeks of chemotherapy completion. The median overall survival in the group was20.7 months with belagenpumatucel-L compared to 13.7months with placebo [HR 0.75; P=0.083]. In patients who had previously received pretreatment radiation, improved median overall survival was shown.[90]

Table 2 some results trials immunotherapy through vaccine development in non-small cell lung cancer

Immunotherapy type	Agent	Phase	Results	Ref
Tumorwhole-cell vaccines	Belagenpumatucel-L	II	†Belagenpumatucel was well-tolerated and provided a survival advantage that warranted perusal of a phase III trial	89
	Belagenpumatucel-L	III	‡Patients receiving belagenpumatucel showed a clinically meaningful greater overall survival vs. placebo	90
Antigen-specific vaccines	MAGE-A3	II	MAGE-A3demonstrated relative improvement in disease-free interval and disease-free survival prompting phase III evaluation	91
MAGRIT	MAGE-A3	III	MAGE-A3 as an adjuvant did not improve disease-free survival vs. placebo	92
	L-BLP25	IIb	Patients receiving L-BLP25 + best supportive care (BSC) vs. BSC alone demonstrated longer survival time	93,94
START	L-BLP25	III	Overall survival was not statistically significant between L-BLP25 and placebo, however L-BLP25 + concurrent chemotherapy + radiation showed survival advantage vs. placebo prompting a new phase III trial	95
START2		III	Ongoing trial investigating overall survival in patients with concurrent chemo radiation + L-BLP25 or control	95
	CIMAVax EGFEGF-based	II	Direct correlation between antibody response and survival and between a decrease in serum EGF and survival when vaccinated with EGF	96
	TG4010 + standard chemotherapy	II	Patients vaccinated with TG4010 had a MUC1-sepcific cellular response	97
	TG4010+standard chemotherapy	IIb	6-month progression-free survival was increased in the TG4010 + chemotherapy group vs. chemotherapy alone demonstrating that TG4010 may enhance the effects of chemotherapy	98

†, patients experienced a dose-related survival advantage when they received at least 2.5×107 cells per injection over a course of up to a maximum of 16 injections; ‡, patients who received the vaccine within 12 weeks of the end of front line therapy showed increased survival;EGF, epidermal growth factor; MAGE-A3, Melanoma-associated antigen-A3; L-BLP25, Liposomal BLP25

Antigen-specific vaccines

Melanoma-associated antigen-A3 [MAGE-A3]

MAGE-A3 is primarily expressed on tumor cells [35%of NSCLCs express it] but not on normal cells except testicular germ cells and placental trophoblast.[88], where its increased expression is connected with advanced disease and poor prognosis.[103]·In a multicenter, double-blinded phase II clinical trial, the efficacy of MAGE-A3 as a tumor-specific vaccine target in NSCLC was evaluated for tolerability and efficacy [91].One hundred eighty-two patients with completely resectedMAGE-A3 [+] stage pib OR PII were assigned in a 2:1 ratio to receive postoperative recombinant MAGE-A3 protein plus adjuvant or placebo. Patients were vaccinated for a total of five cycles every three weeks followed by 8 vaccinations every three months. The primary endpoint of this study was disease-free interval and other endpoints included safety, disease-free survival, and overall survival. After a median follow-up of 28 months, group comparisons of disease-free survival and overall survival were 0.73 [95% CI: 0.45–1.16] and 0.66 [95% CI: 0.36–1.20], respectively. The results of the study showed a positive trend for activity of MAGE-A3in the treatment of NSCLC with improvement of disease free interval and disease-free survival of 27%. Although this improvement was not statistically significant, the ability of the results prompted the development of a phase III trial named MAGRIT [MAGE-A3 as Adjuvant Non-Small Cell Lung Cancer Immunotherapy].The MAGRIT trial evaluated disease-free survival and overall survival, yearly disease-free survival from 2–5 years, lung cancer specific survival, disease-free specific survival, and adverse events in curatively resected patients whose lung cancers were MAGE-A3 positive. There were 2,270patients who were stage IB, II, and IIIA and assigned to either the MAGE-A3 or placebo group. MAGE-A3 as an adjuvant treatment did not increase disease-free survival compared to placebo in the overall population or in the patients who did not get chemotherapy [92]. While the trial did not meet its primary endpoint; the MAGRITtrial helps confirm that vaccines are well tolerated with mild effects and no apparent increase in immune-mediated disorders.

Liposo Liposomal BLP25 (L-BLP25)

Liposomal BLP25 [L-BLP25] is a peptide-based vaccine that targets the exposed core peptide of a membrane associated glycoprotein [MUC1], which is commonly found on the apical surface of most epithelial cells of the respiratory, genitourinary, and digestive system. WhenMUC1 becomes aberrantly glycosylated; it becomes immunologically different from the MUC1 on normal cells. Overexpression of MUC1 is associated with approximately60%

of lung cancers and is also associated with greater immunosuppression and a poorer prognosis in patients with adenocarcinoma.[104].

The effects of the L-BLP25 vaccine on survival and toxicity were evaluated in a randomized phase IIb studying patients with stage IIIB and IV NSCLC. Patients were randomized into the L-BLP25 plus best supportive care [BSC] or BSC alone group, with the groups having 88 and 83 patients, respectively. Patients in the L-BLP25 plus BSC group had a median survival time of 4.4 months longer than the patients in the BSC alone group.[93]. Further results from updated survival analysis indicated a median survival time of 17.2 months and a 31% 3-year survival rate in patients in the L-BLP25 plus BSC arm comparedto13.0 months and 17% 3-year survival rate in the group of patients receiving BSC alone.[94]

A phase III trial [START] was undertaken based on the results of the phase IIb study. Patients [n=1,513] with unresectable stage III NSCLC who did not progress after primary chemo-radiotherapy were randomized 2:1 to get either L-BLP25 or placebo. Despite L-BLP25being well tolerated, the START trial failed to meet its primary efficacy endpoint. However, there was a significant survival advantage in those patients treated with L-BLP25and concurrent chemotherapy and radiation.[95].

CIMAVax EGF

This vaccine was developed for the treatment of advanced stages IIIB and IV NSCLC after first-line chemotherapy. It was developed and is currently approved for use in Cuba, Peru, and Venezuela. It was developed from human recombinant EGF conjugated to the P64K Neisseria meningitides recombinant protein.[96]

Revaccination treatment with cyclophosphamide was evaluated in a pilot trial with the role of cyclophosphamide being to reduce inhibition of T-suppressor cells. Throughout the trials, serial antibody measurements of EGF were done through an enzyme-linked immunosorbent assay [ELISA] and were stratified based on their measurement; a good antibody responder produced an antibody response to titer greater than 1:4,000 and a poor antibody responder had a titer less than 1:4,000. The results of the pooled trials showed that there was no significant difference in antibody responses with the pretreatment of cyclophosphamide prior to EGF administration. The use of ISA 51 rather than aluminum hydroxide promoted a significant difference in the number of antibody responders. Thus, there appears to be a survival time relationship with anti-EGF antibody titers and immune response duration [105].

A phase II trial evaluating the immunogenicity safety and effect on survival of EGF-based cancer vaccine included80 patients with stage IIIB/IV NSCLC after completing first-line chemotherapy.[96]. Patients were randomly assigned to receive best supportive care or EGF vaccinations. Good antibody responders who were vaccinated had a longer median overall survival of 11.7 months compared to 3.6 months in vaccinated, poor antibody responders. A longer median overall was found in vaccinated patients with serum EGF levels below 168 pg./mL versus 5.6 months in vaccinated patients whose serum EGF levels were greater than 168 pg./mL. The results of the trial showed a trend toward increased overall survival for vaccinated patients; this was found to be statistically significant in the subgroup of patients younger than the age of 60 versus patients over the age of 60 [11.57and 5.33 months respectively, P=0.124]. There was a direct connection between a decrease in serum EGF levels and survival and a correlation between antibody response and survival.

TG4010 [MVA-MUC1-IL-2] vaccine

Like the L-BLP25 vaccine, TG4010 targets the MUC1antigen on malignant cells but uses a recombinant vaccine virus [modified virus of Ankara or MVA] that encodes human MUC1 and IL-2. There was induced expression of MUC1 on the cell surface after the transduction of peripheral blood mononuclear cells gotten from healthy donors with MVA-MUC1-IL-2 [106].In a phase II randomized, open-label study, two schedules of TG4010 combined with first-line chemotherapy were compared in patients with stage IIIB/IV NSCLC. In arm1 [n=44] TG4010 was combined with cisplatin [100 mg/m2day 1] and vinorelbine [25 mg/m2 days 1 and 8] while in arm2 [n=21] patients were treated with TG4010 monotherapyuntil disease progression, followed by TG4010 plus the same chemotherapy as in arm 1. Median survivals for arms 1and 2 were 12.7 and 14.9 months, respectively. Patient's with detectable CD8 T cell response also showed detectable immune responses against MUC1 antigen and showed increased time to tumor progression and longer median survival when compared to patients with no detectable CD8T cell response. This study showed that the vaccine had aMUC1-specific cellular immune response.[97]

A larger phase IIb trial was developed to evaluate 6-monthprogression-free survival with a target rate of 40% or higher in the experimental group.[98]. One hundred and forty-eight patients with stage IIIB/IV NSCLC expressingMUC1 immunohistochemistry were enrolled in the study. Seventy-four patients were allocated to the combination therapy group and received TG4010 plus cisplatin and gemcitabine for up to six cycles, and another 74 patients

received only chemotherapy. Comparing the progression free survival at 6 months between patients in the TG4010with chemotherapy arm and those in the chemotherapyalonearm, the results did not differ significantly [43.2 % [95% CI: 33.4–53.5%] and 35.1% [95% CI: 25.9–45.3%], respectively, P=0.307]. Median overall survival for patients in the TG4010 was 10.7 months [95% CI: 8.8–18.0] and10.3 months in the chemotherapy-alone group [95% CI: 8.3–12.5]; these results failed to show statistical significance. Longer median overall survival was found in patients who had an objective response to TG4010 based on the World Health Organization [WHO] imaging criteria. Common side effects in the TG4010 group included fever, abdominal pain, and injection-site pain of any grade, following the National Cancer Institute Common Toxicity Criteria. Using these criteria, the rates of serious adverse events did not differ significantly between the TG4010group and chemotherapy-alone group [52.1% and 47.2%, respectively]. A shorter median overall survival and increased rates of adverse events were found in patients with increased numbers of activated CD16+, CD56+, CD69+, and natural killer cells measured before treatments when compared to patients with normal natural killer cell populations.

CONCLUSION

Important progresses have been made toward reduction health hazard connected with to lung cancer. Particularly smoking, and for the inhibition of several disorder in current decade, target therapy and immunotherapy have mad obvious contribution to enhanced controlling of the lung cancer, additionally, genetic and biomarkers testing are helping in the personalized management of the several form of lung cancer .through personalized management of NSCLC, treatment are individual and target specific mutation with great precision with aim of lengthening progresses – free survival. Immunotherapy present the idea of improving and guiding the body own immune defense to target the cancer cell. There existing clinical trial investigation the use of vaccines to treat NSCLC .because lung cancer causes more death in china and united state then any other cancer, research is continuously being followed to grow.

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