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The Application and Progress of Immune Checkpoint Inhibitors in the Immunotherapy of Non-Small Cell Lung Cancer

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Abstract

For several years now, the therapeutic situation in the management of non-small cell lung cancer using the immunotherapy protocol has allowed the approval of several drugs. These different drugs have shown fantastic results but with the downside of some side effects whether in monotherapy or in dual therapy with chemotherapy or radiotherapy.

The aim of our work was to review the different drugs administered in first- or second-line therapy for non-small cell lung cancer and other drugs that are still in clinical research or have been dropped. In view of all this, the vaccine is being considered, but its application is still very much in doubt in the scientific community.

Keywords: Non-small cell lung cancer (NSCLC); combination strategy; programmed death-1 (PD-1); programmed death ligand-1 (PD-L1); immune checkpoint inhibitor

Introduction

Chemotherapy and Radiation therapy have been successful in reversing non-small cell lung cancer (NSCLC) prognostic [1, 2], but patients inevitably suffer from drug resistance and toxicity, and sometimes relapse. In this context, immunotherapy offers patients a fantastic life-saving prognosis. In this review, we aim to prove the application and progress of immune checkpoint inhibitors in the immunotherapy of non-small cell lung cancer.

Immunotherapy is the use of natural or synthetic substances to alter the behavior of immune cells to better respond to or interact with cancer cells to destroy them.

Immune checkpoint inhibitors (ICIs) targeting programmed death receptor 1 (PD-1), programmed cell death receptor ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) have shown significant anti-tumour efficacy, produced durable clinical responses and prolonged survival by regulating T-cell-mediated immunological responses in patients with advanced/refractory and metastatic NSCLC in clinical trials. Knowledge of these various advances in the application of immune checkpoint inhibitors in NSCLC immunotherapy will supply insight into the critical role of immunotherapy development in the regression of cancers, particularly NSCLC.

Mechanism of PD-1, PD-L1 and CTLA-4

Regarding the mechanism of PD-1, PD-L1 and CTLA4, PD-1 has two mechanisms. The first contributes to the apoptosis of antigen-specific T cells in lymph nodes through 'programmed cell death' (PCD) [3, 4]. The second mechanism contributes to reduced apoptosis of regulatory T cells (Anti-inflammatory and suppressive). Regulatory T-cells. In addition, PD-1 binds to PD-L1 and PD-L2. Engagement of PD-L1 protein on tumor cells inhibits PD-1 expression on effector T cells [5-15]. PD-L1 protein on the tumor cell is associated with reduced survival in pancreatic cancer and other cancers, while showing promotion of immunotherapy. The efficacy of PD-1 on monocytes allows for hyper regulation upon activation by its PD-L1 which introduces production to inhibit CD4 T cells. The suppression of PD1 on CD8+ T cells allows the degree of T cell depletion to be found, for example in infection or cancer [11, 16-24]. Normally, the adaptive immune system responds to antigen with signals due to the presence of endogenous and exogenous danger. The immune system promotes clonal expansion of antigen specific CD8+ T cells and/or CD4+ helper cells by propagation. The binding between PD-L1 and PD-1 transmits a highly inhibitory signal based on the interaction with phosphatases (SHP-1 or SHP-2) via the immune receptor tyrosine-based switching motif (ITSM). Cytotoxic T lymphocyte-associated protein 4 (CTLA4 or CTLA-4) or known as differentiation group 152 allows for the negative regulation of the immune response through its receptor protein. Constitutively expressed in the regulatory T cell, it up regulates the conventional T cell after activation. It acts as an "off" switch when bound to CD80 or CD86 on the surface of antigen presenting cells [1, 3, 4].

Application of immune checkpoint inhibitors in the immunotherapy of non-small cell lung cancer

Anti-PD-1

(Nivolumab, Pembrolizumab, PF-06801591, MEDI0680, Camrelizumab)

PD-1 or CD279 belonging to the CD28 receptor family has a type I transmembrane surface receptor. On the rise of T lymphocytes following stimulation by antigens and responding to cytokines induced by activation of T lymphocytes, these Naive T cells express PD-1 [5]. In addition, PD-1 can be expressed in B lymphocytes, and monocytes. In short, PD-1 reduces the threshold of apoptosis and induces anergy the immune system via the signal from the passivated T cell receptor, which usually leads to depletion of T cells [5].

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Nivolumab

Nivolumab, which has another name, BMS936558, Opdivo, MDX-1106 and ONO-4538, is a humanized anti-PD-1 IgG4 immunoglobulin that has an anti-tumor effect with PD-1 blocking function at PD-L1 / PD-L2 [5] and is used in the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy [6]. Or in combination with ipilimumab as first-line therapy, whose tumor express PD-L1, without EGRF or ALK tumour genomic abnormalities [7].

In general, surgical treatment could increase 5-year OS in patients with early NSCLC, immune modulatory in the favorable strategy for NSCLC treatment [25].

In 2019 (WJOG9616L), a phase II trial of Nivolumab in patients with advanced small cell lung cancer who responded to previous PD-1 / L1 inhibitors had as primary endpoints patients with pathologically proven NSCLC who received systemic anticancer therapy, including immune checkpoint inhibitors, clinical benefit (complete response, partial response or disease control rate> 6 months) was achieved by previous IBIs and progressed, previous IBI was performed> 60 days after registration, ECOG PS 0-1 and with measurable lesions. The response of this trial suggests that patients who responded to the first IBI are likely to respond to a repeat IBI, but there is as yet no convincing evidence to support this hypothesis [5, 9].

Pembrolizumab

Formerly known as MK3475, Keytruda, or lambrolizumab, pembrolizumab is a selective human anti-PD-1 IgG4 monoclonal antibody that blocks the binding of PD-1 to PD-L1 and PD-L2 [6, 7, 10, 11]. Its tolerance and anti-tumor activity in the neo-adjuvant or adjuvant have given particularly satisfactory results in several open studies. Therefore, pembrolizumab has been registered for first-line treatment in patients with metastatic NSCLC with PD-L1 TPS ≥ 50% by the FDA. At the same time, immunotherapy has strong prospects and manageable safety profiles in patients with refractory solid cancers [12, 13, 16, 17].

With the results of this study, we can show that patients with NSCLC and untreated or progressing brain metastases can receive help from systemic pembrolizumab therapy. Although the study was premature, we were able to show that 29 - 7% of patients with PD-L1-positive NSCLC achieved a cerebral metastatic response, allowing the study to meet its primary endpoint [13, 15]. The study considered a total 2-year survival of 34% in this patient cohort exceeding the historically documented survival of 14 - 3% for patients with brain metastases of NSCLC. The study will first focus on the population of patients with brain metastases of lung cancer and to examine the effects of immunotherapy. The other studies show that patients with NSCLC brain metastases can receive help from immunotherapy both as monotherapy 5, 20, 21 and in combination with chemotherapy. Several expanded access programs and studies examining NSCLC patients treated with PD-1 or PD-L1 inhibitors as monotherapy have found comparable results (including activity and safety) in patients with brain metastases compared to those without, highlighting that PD-1 and PD-L1 inhibitors may be active in patients with CNS disease[13, 15].

PF-06801591

The humanized anti-PD1 monoclonal antibody, which binds to the PD-1 receptor and blocks the interaction with PD-1, PF-06801591 is considered safe for its antitumor effect, the pharmacokinetics of which are administered intravenously. or subcutaneously [13, 15]. (PK) of PF-06801591 administered intravenously or subcutaneously, forty patients with locally advanced or metastatic solid tumors were registered from March 2016 to March 2018 in an open multicenter phase I study. Patients received PF-06801591 intravenously at a specified dose of 0.5, 1, 3 or 10 mg / kg every 3 weeks or subcutaneously at a dose of 300 mg every 4 weeks. Studies with PF-06801591 show serious side effects, including fibrillation, intestinal obstruction, upper gastrointestinal bleeding, infected neoplasm, and pelvic fracture [16].

MEDI0680

MEDI0680 formerly known as AMP-514 is a humanized anti-PD-1 [36]. It is an IgG4κ monoclonal antibody whose induction eases the proliferation of peripheral T cells and associated chemokines with the aim of reducing solid tumors. In a phase I dose-escalation, multicenter trial, the safety, efficacy, PK, and pharmacodynamics (PD) of AMP-514 were evaluated in patients (n = 58) with advanced solid malignancies, including non-squamous NSCLC, kidney cancer, and melanoma [16]. Some clinical trials the increase in dose from the early phase of NSCLC expresses side effects such as vomiting, fatigue, asthenia, loss of appetite, abdominal pain, pyrexia, arthralgia, pruritus and asthenia [16, 18].

Camrelizumab

Camrelizumab (AiRuiKa™) is a drug that was developed by Jiangsu Hengrui Medicine Co. Ltd (Jiangsu Hengrui Medicine) which has the reputation of being very high-affinity humanizing anti-programmed cell death 1 (PD) monoclonal IgG4-kappa antibody -1). The authors approved in May 2019 only in China, for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma who have previously received at least two systemic chemotherapies [9, 19, 24]. Currently the recommended dose for better therapeutic management is 200 mg IV once every 2 weeks until intolerable toxicity or disease progression occurs [9, 19, 24-33].

Anti-PD-L1

(Atezolizumab, Durvalumab, Avelumab, BMS-936559, Envafolimab)

PD-L1 is a protein found on tumor cells. T cell helper CD4 + and CD8 + cytotoxic Co inhibitors of PD-1 T cells after activation, the T cells release IFN-γ which allows the PD-L1 protein to rise of the tumor cell [22, 23, 31, 34-45].

Atezolizumab

Atezolizumab, also finding itself as Tecentriq MPDL3280A or RG7446 is a humanized and selective anti-PD-L1 IgG1 monoclonal antibody that has three competencies [45]. First it blocks the interaction of PD-L1 and PD-1, second it blocks the combination of PD-L1 and B7-1 while restoring the immune activity of T cells and third it enhances the effect anti-tumor. Finally, we can report that atezolizumab is a very stable chemotherapeutic drug, has excellent tolerability, being exceptional safety and an unprecedented value for money for the patient in their healing process [22, 23, 31, 45].

Durvalumab

Known by diver's names such as MEDI4736 or Infinzi, durvalumab is an anti-PD L1 IgG1 antibody that has recently been the subject of several studies [11, 13, 14, 31, 46]. A phase III study proved clear prolongations of OS and PFS at 12 months in patients with NSCLC treated with durvalumab. In summary, durvalumab promises better result in combination with radiation therapy or platinum according to

some studies [11, 13, 14, 31, 46].

Avelumab

Avelumab, also known as Bavencio or MSB0010718C is a new all-human antibody that has anti-PD-L1 IgG1 function [22, 23, 37, 46, 47]. In the crystallizable fragment (Fc) of the structure that allows receptors to bind Fc-γ receptors to produce a cytotoxicity on natural killer cells which enables the connection between PD-L1 and B7-1 to be blocked. In conclusion, avelumab is approved as a second treatment choice for NSCLC after platinum-based chemotherapy [22, 23, 37, 46, 47].

BMS-936559

Highly humanized, BMS-936559 or MDX1105 is a monoclonal antibody with high affinity for IgG4 antibodies that has the ability to directly inhibit the binding of PD-L1 to PD-1 and CD86 [14, 29, 35]. In various clinical trials, BMS-936559 or MDX1105 has shown prolonged stability and tolerability in patients with advanced NSCLC [14, 29, 35].

Envafolimab

Designed by crystallizable fragment fusion of human IgG1 antibody structure with the anti-PD-L1 domain. Envafolimab or KN035 is a novel and promising single-domain antibody that binds to PD-L1 with an extremely high binding affinity and specificity for induction of T-cell-mediated immune response and inhibition in tumor growth. There were significant improvements in the OS and the PFS of Envafolimab, which also showed helpful safety profile and preliminary evidence of promising anti-tumor activity in advanced NSCLC patients [22, 23, 35, 37, 46, 47].

Anti-CTLA4

(Ipilimumab, Tremelimumab)

Ipilimumab

The approval of ipilimumab in the management of non-small cell lung cancer is often in combination with drugs such as nivolumab administered with two cycles of platinum-doublet chemotherapy often as first line treatment of patients.

Ipilimumab or Yervoy, MDX-010, MDX-101 is a high-affinity human anti-CTLA-4. It is a monoclonal antibody which, together with conventional combination therapies, can be claimed as a first line treatment for 3 months in NSCLC patients and also has no safety concerns [19, 48, 49].

Tremelimumab

Tremelimumab developed by Pfizer Inc in 2007 is a complete human anti-CTLA-4 monoclonal IgG2 antibody [48, 50–52]. Others clinical trials are in progress, notably on patients with refractory and metastatic melanomas.

A global, multicenter, randomized, open-label trial of Infinzi (durvalumab) in combination with Tremelimumab, versus standard platinum-based chemotherapy in patients with previously untreated stage IV (metastatic) non-small cell lung cancer (NSCLC). The trial was conducted in an all-component population, and the primary analysis population was patients with a high tumour mutation burden (TMB). ("Update on the Phase III NEPTUNE trial of ... - AstraZeneca") TMB is a measure of the number of mutations in the genome (DNA) of a tumour, and tumors with elevated levels of TMB may be more visible to the immune system [48, 50–52].

Combination

For better results, combination therapies are used. As conventional therapeutic combinations, we have chemotherapy, radiotherapy, and anti-angiogenic drugs.

Combined with radiation therapy

Radiotherapy, which excels in controlling the local development of tumors, has proved immune modulatory effects in the preclinical and clinical phases. Radiation therapy can work in two diverse ways. First, as an in-situ vaccine that causes cells presenting local antigens to increase their uptake and presentation of cancerous neo-antigens [5, 9, 10, 12, 26, 27, 53–59]. Second, it acts against the background of a pro-inflammatory cytokine for the release of cytosolic DNA and the stimulation of type I interferon.

One of the first studies of dual therapy between immunotherapy and radiotherapy was conducted in the metastatic phase where radiotherapy only played a metastatic role. In the setting of radiotherapy with anti-iPD-1, a phase 1 KEYNOTE 001 trial examined patients with metastatic NSCLC who were first treated with radiotherapy prior to inoculation of the first dose of pembrolizumab (43 of 97 patients) [5, 9, 10, 12, 26, 27, 53–59]. The results of this trial showed significant improvement in median OS (10.7 versus 5.3 months) and progression-free survival (PFS) in patients who received pembrolizumab followed by RT.

Numerous clinical trials have been conducted to show the combination of CTLA-4 ipilimumab and RT in patients with various solid tumors and we found that eight of the thirty-five patients enrolled suffered from NSCLC. First, the trial directed radiation therapy to the lung or liver injury and second, ipilimumab was administered for two cycles. Ten percent of patients had a partial response (excluding the irradiated lesion) and 23% had a partial response or stable and lasting disease for 6 months. Comparison of irradiation of hepatic damage with lung damage resulted in an increase in CD81 T cells with expression of the inducible T cell co-stimulator, glucocorticoid-induced tumor necrosis factor and gene. activation of lymphocytes three.

The combination of immunotherapy and radiotherapy gives spectacular results in all its facets. However, many questions still stay unanswered, such as the timing of the sequence of events for a good dual therapy to perfect the activation of tumor destruction checkpoints more efficiently [5, 9, 10, 12, 26, 27, 53–59].

Combined with chemical therapy

less than 10 years immunotherapy showed its strength in the effective management of tumor diseases and chemotherapy showed its weaknesses [3]. The first promising results published in 2015 in second-line treatment in combination with chemotherapy have led to the approval of pembrolizumab, atezolizumab and Nivolumab.

In the sign for first-line immunotherapy, pembrolizumab is at the top of the list for full approval in dual therapy (immunotherapy and chemotherapy). On the drug side, only pembrolizumab monotherapy in advanced/metastatic NSCLC with ALK/EGFR has been approved by the FDA. In combination therapy with chemotherapy, only platinum is used as a base.

Common combinations of immunotherapy and chemotherapy are either carboplatin or either paclitaxel or nab-paclitaxel [based on KN407] for scaly patients, and carboplatin or cisplatin and pemetrexed, for non-scaly patients [based on KN189]. With the OMEA guidelines, the combination of atezolizumab/chemotherapy with/without bevacizumab is recommended treatments for any expression of PD-L1 in the treatment algorithm for stage IV NSCLC.

In addition, Camrelizumab has become the standard treatment plan recommended by lung cancer guidelines CSCO for biotherapy.

The unique molecular biology structure of Camrelizumab [10], Erika has lower IC50 and EC50 values; Camrelizumab in combination with pemetrexed/carboplatin has significant clinical advantages in the first-line treatment of patients with advanced EGFR/ALK wild-type non-scaly NSCLC. Median PFS is as high as 11.3 months, ORR can be as high as 60% and OS has not been achieved and should be one of the new standards first-line treatment options for this population; Camrelizumab has completed several clinical studies in lung cancer and hopes to cure more patients [1–20].

Combined with Anti-Angiogenic Drugs (AAD)

VEGF which is mediated by angiogenesis is especially important for tumour growth and metastasis and whose pathways of tumour angiogenesis are targets of set up therapeutic treatments in NSCLC Inhibition of angiogenesis in NSCLC therapeutics is summarized by two main strategies: monoclonal antibodies targeting VEGF (bevacizumab) or VEGFR (ramucirumab) or small molecule TKIs that inhibit multiple angiogenic and proliferative pathways (nintedanib). For several years, scientific curiosity has highlighted the complexity of the immune system in certain mechanisms for a more explicit understanding of immunosurveillance in correlation with checkpoint inhibitors. In this respect, a large number of phase III studies show the success of combining immunotherapy with anti-angiogenic drugs. These trials show an intertwined regulation of VEGF signaling and immunosuppression in the tumour microenvironment suggesting that the combination of anti-VEGF agents and immune checkpoint blockade may have synergistic antitumor activity, as well as favorable tolerance. A November 2017 study NCT01454102 with primary focus on safety and tolerability of Nivolumab + chemotherapy, Relevant regimens (immunotherapy + angiogenesis inhibitor in NSCLC), Cohort D: maintenance of nivolumab + bevacizumab had satisfactory results [21, 60–62].

The side effect of immunotherapy

Although immunotherapy is intended to strengthen the immune system to neutralize cancer cells, it has significant side effects. The side effect can occur as early as 1-3 weeks and if several months after the end of treatment. Immunotherapy may take longer to achieve a response than conventional chemotherapy, and patients may have stable disease or even progression after first treatment before improvement is seen. In addition, side effects tend to be characterised by inflammation and require vigilance in observation and reporting to providers to ease prompt intervention. Patients should be aware of these unique responses attributed to immunotherapy as they may be unexpected.

we can list as side effects on the gastrointestinal, pulmonary, endocrine, and even cutaneous.

Gastrointestinal

Gastrointestinal irAEs are an important side effect of CPIs, occurring in 44% of patients receiving anti-CTLA-4/anti-PD-1 combination therapy, 23-33% of patients receiving anti-CTLA-4 therapy and <20% of patients receiving anti-PD-1 monotherapy. Symptoms, including diarrhoea, abdominal pain and sometimes pyrexia, occur on average after three infusions, although they may occur earlier during treatment or even months after discontinuation of checkpoint therapy. Like the endoscopic appearance of colitis due to inflammatory bowel disease, these appearances may be diffuse or occur in segments. Although a complete mechanism has not yet been elucidated, at least two typical histological aspects have been reported: neutrophilic infiltration in micro-abscesses and epithelial cell atrophy leading to crypt atrophy, or lymphocytic infiltration into the epithelium in response to epithelial injury. The small intestine may be rarely involved, and cases of enteritis have been confirmed by CT scan after combined therapy. The upper gastrointestinal tract may also be affected, but less often. The most obvious mucositis in terms of appearance may manifest as inflammation of the lips or mouth which, if severe, may affect oral intake and require nutritional supplementation. Cases of oesophagitis and gastritis may present non-specifically with nausea and anorexia, with confirmation by endoscopy. General treatment strategies include discontinuation of therapy, fluid replacement and usually glucocorticoids. In the phase 3 Checkmate 067 study, this was sufficient to resolve three cases of grade 3-4 diarrhoea. It is especially important to confirm the diagnosis with a detailed history and endoscopic analysis before starting treatment, as the management of upper gastrointestinal pathology such as gastritis due to non-immunotherapy causes does not normally include steroids. In rare cases, escalation to other immunosuppressive agents or even surgery is necessary [2, 8, 15, 45, 63].

Pulmonary

Immune-mediated pneumonitis is described as a non-infectious inflammation of the lining of the lung with associated interstitial or alveolar infiltrations. ("Immune Checkpoint Inhibitors: An ... - PubMed Central (PMC)") This side effect is not as prevalent as colitis or hepatitis, but it is associated with morbidity and mortality and often leads to discontinuation of treatment. Pulmonary toxicity is uncommon in patients treated with ipilimumab. For patients treated with anti-PD-1 therapy, the overall incidence rate of pneumonitis is 9%. Pneumonitis may occur at any point during and after treatment. Reduced lung reserve due to pre-existing lung disease and chest radiotherapy may increase the risk of developing pneumonitis. The diagnosis of pneumonitis is based on clinical presentation and radiographic imaging. ("Immune Checkpoint Inhibitors: An ... - PubMed Central (PMC)") Clinical signs and symptoms include dyspnoea, cough, fatigue, hypoxia, chest pain, and haemoptysis. The severity of symptoms varies among patients and often mimics other common respiratory illnesses. Radiographic findings of diffuse infiltrates, lobular nodularity with air trapping, and interstitial fibrosis support the diagnosis. ("Immune Checkpoint Inhibitors: An ... - PubMed Central (PMC)") In patients treated with anti-PD-1 therapy, microscopic findings include diffuse lymphocytic infiltrates, while in limited reports of ipilimumab-induced pneumonitis, histologic findings were described as sarcoid-like granulomatous reactions with macrophages surrounded by inflammation. Caring considerations include the assessment of and education of patients and families to report on changes in pulmonary function, including shortness of breath, coughing, chest pain, and fever. ("Immune Checkpoint Inhibitors: An ... - PubMed Central (PMC)") ("Immune Checkpoint Inhibitors: An ... - PubMed Central (PMC)") In severe cases, corticosteroid or oxygen therapy may be needed [8, 15, 34, 45, 63].

Endocrine

About 10% of patients treated with anti-CTLA-4 experience clinically significant endocrinopathy, while the incidence of endocrine disorders in patients treated with nivolumab is 14%, with 2% of events grade 3–4 in severity. Less than 5% of patients experienced grade 3–4 endocrine toxicity with combination treatment. The main types of endocrine toxicity derive from inflammation of the thyroid, pituitary, or adrenal glands and are often difficult to find because they typically present with non-specific symptoms, such as fatigue, nausea, headache,

and visual changes [8, 15, 34, 45, 63].

Cutaneous

"The most common cutaneous toxicities include pruritus and maculopapular rash." ("Immune Checkpoint Inhibitors: An ... - PubMed Central (PMC)") Cases of immune-mediated cutaneous toxicities include vitiligo, Stevens–Johnson syndrome, Sweet's syndrome, toxic epidermal necrolysis, bullous pemphigoid, and lichen sclerosis. Rash and pruritus occur early and are seen in 50% of all patients treated with ipilimumab as compared to 28%–37% in patients treated with nivolumab and pembrolizumab, respectively. ("Immune Checkpoint Inhibitors: An ... - PubMed Central (PMC)") Patients with suspected Stevens–Johnson syndrome or toxic epidermal necrolysis require immediate hospitalization. The offending agent should be dropped in these instances [2, 8, 15, 31, 41, 43, 45, 50, 63].

In the first lines of treatment allows more patients to potentially benefit. One of the theoretical concerns about using neo adjuvant therapy, whether it's chemotherapy, targeted therapy, or immunotherapy, or a combination of those, is the fear of creating toxicity that would prevent the patient from having surgery and intense treatment. That's obviously something we want to be close to [a] never event. There have been many studies that have looked at this over time. There's the NADIM study in Spain, which looked at chemotherapy and nivolumab [Opdivo]. The NEOSTAR study looked at a combination of pure OI [immunotherapy] with nivolumab and ipilimumab [Yervoy]. The LCMC3 study, which looked at neoadjuvant atezolizumab [Tecentriq], is probably the strongest data set, at least. It's the one that's had the most presentations recently because of the hype around the data. CheckMate 816, it was a phase III study with nivolumab and chemotherapy in the neoadjuvant setting versus chemotherapy alone and [in] the neoadjuvant setting, it was 3 cycles of neo adjuvant chemo immunotherapy. We found a pathologic complete response rate of 24%, independent of PD-L1 [programmed death-ligand 1] status, with integrated immunotherapy. Without immunotherapy, with chemo alone, the pathologic complete response rate is about 2%, which is interesting. We don't have mature survival data yet, but that difference in pathologic complete responses is very striking. And one of the most striking differences that we've seen. And I think most recently at ASCO, we saw some of the presentations around surgical outcomes. Dr. Forb presented some of the work on pathologic complete response. Dr. Spice presented some of the work around surgical outcomes, and not only did neo adjuvant chemo immunotherapy not create problems in terms of surgical intervention, but it also improved surgical outcomes, which went from a theoretical weakness to strength of chemo immunotherapy use. Not only were patients used on more quickly, but more patients underwent lobectomy than pneumonectomy. Pneumonectomy is a much more morbid surgery. Patients have fewer complications with neo adjuvant chemo immunotherapy, probably because the tumor has shrunk. The operation has been made easier. Operating time has been reduced in the operating room. Many virtuous surgical outcomes that really took what was a theoretical concern around drugs in neo adjuvant [neo adjuvant/adjuvant] chemo immunotherapy. That approach has shown its strength. So, I think we're still waiting for the survival data, but it's extremely provocative in terms of pathologic complete response rates. And it looks workable and safe based on the surgical outcomes that we've seen to date.

Discussion

Immunotherapy has revolutionized the therapeutic landscape of NSCLC, whether as monotherapy or dual therapy. For this reason, the role of this therapy in localized disease is currently being studied in great detail, with the promise of breathtaking results. However, the administration of immunotherapy is complexes, but the ultimate goal is the total remission of the patient with fewer side effects. In this respect, biomarkers have distinct roles in the treatment process [3, 63]. Furthermore, we have to find the best way to combine it with RT and/or chemotherapy, which is not an easy task, partly because there are still many unresolved questions in this area. In the studies many of the latest generation drugs with side effects are gaining an especially prominent place because of their ease of production, for example camrelizumab. We are currently awaiting the results of several trials evaluating the role of PD-1 axis blocking immunotherapy as an adjuvant therapy, although the vaccine-based strategy has failed to prove a survival benefit. In neo adjuvant immunotherapy, the combination of CT and immunotherapy are more promising than immunotherapy alone, significantly increasing CPR rates. The studies conducted to date leave many questions unresolved, including the lack of predictive biomarkers and the fact that we still do not know how to optimally assess radiological response or best duration. However, we fully expect that ongoing trials will prove a benefit of immunotherapy in early-stage disease as well. In summary, it seems clear that immunotherapy (at least in patients without driver mutations) will inevitably become part of the therapeutic armamentarium for early NSCLC soon, based on the promising results of the studies published so far and the many ongoing trials.

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