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Neoadjuvant Targeted Therapies for Non-Small Cell Lung Cancer from the Surgical Perspective

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Abstract

Non-small cell lung cancer is the main type of lung cancer which is the broadest and deadliest cancer worldwide. Despite improvements in treatment approaches and diagnosis programs, the expected survival rate for non-small cell lung cancer has still not been reached. The heterogeneous and case-based nature of non-small cell lung cancer plays a role in lower-than-expected success rates. Neoadjuvant treatment approaches are suggested to increase the success of surgical treatment. However, conventional neoadjuvant strategies cannot provide the expected success rate due to the heterogeneous and complicated molecular pathogenesis of non-small cell lung cancer. Case-based treatment settings are required to overcome these features of non-small cell lung cancer and achieve a better outcome in treatment. In this review, the feasibility and oncological benefits of using neoadjuvant targeted therapies, which have developed in recent years and provide case-based treatment approaches, are discussed from the perspective of the surgeon.

Keywords: Preoperative period, molecular targeted therapy, non-small cell lung cancer, angiogenesis inhibitors, protein kinase inhibitors, personalized medicine

Introduction

Lung cancer is the deadliest cancer worldwide, which is responsible for 1.8 million deaths (18.4% of total cancer deaths).[1] Also, this death toll is more than the second deadliest cancer (colorectal cancer is responsible for 881 000 deaths) plus the third deadliest cancer (stomach cancer is responsible for 783 000 deaths).[1] Unfortunately, lung cancer, the deadliest cancer, is also one of the most prevalent cancers worldwide.[1] For lung cancer, almost 2.1 million (11.6% of the total cancer incidence burden) diagnoses were made to be estimated in 2018.[1] Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancers.[3] Despite revolutionary developments in treatment and early diagnosis programs, the overall survival (OS) rate for NSCLC is not as high as expected.[2] The 5-year survival rate for the early localized stage is 59%, 31.7% for the regional metastatic stage, and 5.8% for the distant metastatic stage.[2] The poor outcome depends on the complex structure and individual features of NSCLC. Recently, researchers focus the improved and individualized therapies for better outcomes.[4]

Treatment of NSCLC is a complicated process including distinct options such as surgery, chemotherapy, or radiotherapy.[3] In general, surgical treatment is the optimal option for patients who can tolerate surgery.[3] Surgical treatment may be the most successful option, but many patients are not cured and many have recurrences.[5] Zhu et al[5] conducted a retrospective study with patients with early-stage NSCLC reporting that the 1-, 3-, 5-, and 10-year postoperative recurrence rates were 82.0%, 67.0%, 59.0%, and 48.0%, respectively. That shows that surgical treatment needs to be supported preoperatively and postoperatively to improve recurrence-free survival and OS of patients.

The oncological benefits of preoperative treatment include the reduced recurrence rate by eliminating micrometastases and increased operability of tumors.[8] A meta-analysis of 15 randomized controlled trials with 2385 NSCLC patients showed that preoperative chemotherapy reduced the relative risk of death by 13% while also improving the 5-year survival rate by 5% (from 40% to 45%).[6] Another study supporting this evidence with 988 patients from 2006 showed that preoperative chemotherapy increased the OS rate by 6%.[7] Although preoperative chemotherapy improved the outcome of surgical treatments, numerous lung cancer patients still cannot reach the expected treatment success for various and tumor-dependent factors such as genetic alterations.[9]

Non-small cell lung cancer is one of the most heterogeneous cancer.[10] Non-small cell lung cancer cells have various genetic disorders such as epithelial growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) mutations that mutations might be promise therapeutic targets.[10] In recent years, several targeted therapy studies have been conducted for advanced-stage NSCLC.[10] In addition, there are studies conducted for localized NSCLC in the perioperative period.[11] In this review, unlike other studies, we analyzed studies related to targeted therapies used as a neoadjuvant in the preoperative period. We aimed to reach new perspectives as surgeon for better outcomes.

Preoperative Anti-Angiogenic Therapies

The term "angiogenesis" refers to the physiological process of the development of new blood vessels from pre-existing blood vessels.[12] The process primarily occurs at embryonic and fetal stages; however, it also occurs in adult physiological events such as the menstrual cycle, wound healing, and organ lining regeneration.[12] Furthermore, angiogenesis is one of the basic steps of

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carcinogenesis and tumor progression.[12] Angiogenesis is essential for tumor growth, tumor cell proliferation, and metastasis due to providing nutrients and oxygen for tumor cells.[13] In addition, post angiogenic vessels permeability is abnormal that altered permeability decreases drug delivery hence angiogenesis contributes to drug resistance.[13]

The pro-angiogenic growth factors and cytokines lead to angiogenesis.[14] Tumor cells and tumor-associated cells secrete those particles under hypoxic conditions.[14] Vascular endothelial growth factor (VEGF) is the prepotent pro-angiogenic growth factor.[15] Vascular endothelial growth factor family is composed of five members (VEGF-A, VEGF-B, VEGF-C, VEGF-D, and PlGF) that are ligands for vascular endothelial growth factor receptor (VEGFR),[1-3] which is a kind of tyrosine kinase (TK) receptor family.[15] Vascular endothelial growth factor A is the main angiogenic growth factor in adults and binds to VEGFR2. The VEGFA-VEGFR2 signaling pathway is crucial in tumor growth and related to poor prognosis in many cancers.[16] Zhan et al[17] concluded that VEGF expression is a prognostic factor in NSCLC. In addition, it has been demonstrated that VEGFA-VEGFR2 signaling is not only a prognostic indicator, but it is also a therapeutical target in NSCLC.[18]

Bevacizumab has been developed to target the VEGF/VEGFR signaling pathway.[19] Bevacizumab is a recombinant humanized IgG1 monoclonal antibody.[19] It blocks VEGF-A/VEGFR1-2 signaling pathway by inhibiting VEGF-A.[19] In 2004, the Food and Drug Administration (FDA) approved bevacizumab for clinical use, making itself the first clinically used angiogenesis inhibitor.[19] That angiogenesis inhibitor started to be used in many cancers such as NSCLC.[20] Bevacizumab has been preferentially used in the treatment of non-resectable advanced-stage NSCLC; however, studies demonstrate that it can also be used in resectable patients in a neoadjuvant setting[21] (Table 1).

In 2019, Imai et al[22] conducted a phase II trial of carboplatin–paclitaxel plus bevacizumab in 29 patients with stage IIIA to IV NSCLC patients. As a result of that study, the overall response rate was 72.4% and the complete resection rate was reported to be 70% in patients who underwent surgery.[22] According to Bertino et al.[23] 40% partial pathological response was observed in 5 patients receiving preoperative bevacizumab with the combination of paclitaxel–carboplatin. Despite the administration of bevacizumab, bleeding complication was not noted. In 2013, Chaft et al[24] reported a phase II trial in 50 patients that included resectable NSCLC. In this study, patients were treated with bevacizumab only for 2 weeks. Then, they were administered bevacizumab plus cisplatin–docetaxel followed by surgical resection.[24] In this trial, bevacizumab-related adverse events occurred in 12%, whereas downstaging was noted in 38% of patients.[24] Complete resection rate was 82% who underwent surgery (41 patients). Interestingly,[24] 18% of patients who had bevacizumab developed new intratumoral cavitation, which could be a surrogate marker for the improved pathological response (57% vs. 21%).[24] In this study, a >10% reduction in tumor size was observed after 2 weeks of single-agent bevacizumab administration in 6 out of 11 patients. Among those, postoperative upper gastrointestinal (GI) bleeding occurred in 1 patient and 1 patient developed hemoptysis preoperatively.[25] No bevacizumab-related operative complications were observed.[25]

The use of bevacizumab in the preoperative phase is feasible and well-tolerated, with oncological benefits such as improved tumor regression and improved pathological response rate. According to these features, bevacizumab makes itself a potential preoperative targeted treatment agent.

Use of Tyrosine Kinase Inhibitors in the Preoperative Period

Epithelial growth factor receptor, known as ErbB1, is a transmembrane TK receptor and a member of the ErbB[1-4] family.[26] It can be autophosphorylated and is involved in PI3K/AKT and Ras/MAPK signal pathways.[26] Those signal pathways stimulate significant malignant features such as tumor cell proliferation, angiogenesis, invasion, and tumor cell survival.[26] This signaling profile of EGFR has attracted attention against many cancer types such as glioblastoma.[26] And in numerous cancer types, overexpression and genetic alterations have been detected at different levels.[26]

Epithelial growth factor receptor mutations are the second most common mutated oncogene in lung adenocarcinomas after Kras mutations.[27] Generally, EGFR mutations and aberrant activations occur in exons 19 or 21 that are encoding the TK domain in NSCLC.[28] These mutations and abnormal expression profiles are detected in approximately 14% of Whites and approximately 32% of Asians and are more common in non-smokers and female patients.[28] As a result, EGFR mutations play a role in carcinogenesis and are prevalent in NSCLC; therefore, there has been a focus on targeting the EGFR mutations.[29]

Erlotinib is one of the first-generation TK inhibitors, which has been approved by the United States FDA in advanced-stage NSCLC and metastatic pancreas tumors.[30] Erlotinib blocks the TK domain of EGFR, in this way down signaling pathways those involved in carcinogenesis.[30] Cappuzzo et al[31] conducted a multicenter, randomized, placebo-controlled phase 3 study with 884 analyzable advanced NSCLC patients. They found that erlotinib was well tolerated by patients and improved PSF by 10.8%.[31] Furthermore, erlotinib was found to be used as an adjuvant therapy agent in the early-stage lung cancer.[32] In 2018, Pennell et al[32] showed in a phase II trial that adjuvant erlotinib therapy improved 2-year DFS compared with that of historical controls. There are studies that showed that erlotinib, which is generally used in advanced-stage NSCLC, could also be used in resectable NSCLC neoadjuvant therapy (Table 2).

In 2012, Schaake et al[33] studied the neoadjuvant erlotinib's benefits and toxicity with 60 NSCLC patients. They found that 5% of patients had more than 95% tumor necrosis and 27% of patients showed a partial metabolic response. Moreover, 23% of patients

Table 1. Bevacizumab as a Single Agent in Neoadjuvant Therapy

First Author	Year	Number of Patients	Stage	Targeted Therapy Agent	Reference
Chaft	2013	50	Resectable nonsquamous non-small cell lung cancers	Bevacizumab	24
Imai	2019	29	Stage IIIA to IV nonsquamous non-small cell lung cancer	Bevacizumab	22
Rizvi	2007	19	Resectable IB-IIIA	Bevacizumab	25
Bertino	2011	6	Resectable non-small cell lung cancers	Bevacizumab	23

Table 2. Erlotinib in Resectable-Stage Neoadjuvant Therapy

First Author	Year	Number of Patients	Stages	Targeted Therapy Agent	Reference
Xiong	2019	19	Stage IIIA (N2)	Erlotinib	35
Schaake	2012	60	Early-stage NSCLC	Erlotinib	33
Sacher	2016	22	Early-stage non-small cell lung cancer	Erlotinib	34
Zhong	2019	71	Stage IIIA-N2	Erlotinib	36
Xiong	2020	31	stage IIIA NSCLC	Erlotinib	37

NSCLC, non-small cell lung cancer.

showed more than 50% necrosis.[33] After few years in 2016, Sache et al[34] reported the results of a window of opportunity study with 22 early-stage NSCLC patients. In this study, partial response showed by PET-CT was observed in 2 patients (9%), a minor reduction in 8 patients, necrosis in 8 patients, and fibrosis in 18 patients.[34] Only 4 patients showed grade-III adverse events, and grade-IV adverse event was notified in only 1 patient.[34] Xiong et al[35] conducted a prospective, single-arm, phase II study with stage IIIA-N2 EGFR mutation-positive NSCLC patients. Of 19 patients who received neoadjuvant erlotinib, 14 were operable, and the rate of radical resection in the general population was 68.4%.[35] Pathological downstaging from N2 to N1/N0 was seen in 35.7% of surgical patients and 50% had tumor reduction.[35] Another study that was published in 2019 on the effects of adjuvant erlotinib in patients with stage III NSCLC indicated that although there was a significant improvement in PSF, there was no improvement in the objective response rate.[36] In 2020, Xiong et al[37] found that 67% of patients with EGFR mutation receiving erlotinib as neoadjuvant therapy had a clinical response and pathological response (this rate was 38% in patients who received neoadjuvant chemotherapy) and had an OS was 51.0 months (OS for patients receiving chemotherapy was 20.9 months). In addition, patients receiving erlotinib had significantly major reductions in tumor diameter, serum carcinoembryonic level, and a maximum allelic fraction.

Gefitinib is a small molecule inhibitor derived from synthetic anilinoquinazoline with a molecular weight of 447.[38] It is a potent and selective ATP competitive TK inhibitor.[38] Gefitinib targets the EGFR TK domain, thereby blocking EGFR pathways that promote the features of malignancy such as tumor cell proliferation.[39] In preclinical trials, gefitinib demonstrated anticancer efficacy in various cancers such as colon, breast, and ovarian cancers.[39] Furthermore, on May 5, 2003, gefitinib has been received accelerated approval by FDA as monotherapy for patients with locally advanced or metastatic NSCLC after the failure of chemotherapies (as a second-line therapeutic).[39] Although gefitinib has been used in patients with inoperable-unresectable NSCLC, there are several studies and clinical trials showing that it can be used as a neoadjuvant in the preoperative period (Table 3).

As a result of a phase II trial in 2009, Lara-Guerra et al[40] reported partial response in 4 patients (11%) with the use of preoperative administration of gefitinib in patients with stage 1 NSCLC, disease progression in 3 patients (9%), observable response in all patients with EGFR mutations, and partial response in 50% of patients with EGFR mutations. Three patients had grade III adverse events.[40] Two years later, in 2011, Rizvi et al[41] published a study using gefitinib preoperatively in patients with resectable stage I-II NSCLC.[41] In this study, authors observed a two-sided response of ≥25% in 21/50 (42%) patients and 80.95% (17/21) of patients with re EGFR mutations. Moreover, only 1 patient had a grade-III adverse event and 2 patients had a grade-II adverse event.[41] As results of a phase II single-arm conducted by Zhang et al[42] conducted in resectable stage II-IIIA NSCLC patients, the objective response rate was 54% and the complete response rate was 12.1%.[42] However, no radiological response was observed. In addition, the major pathological response rate was 24.2% and patients with major pathological responses had significantly better DFS than that of other patients.[42]

In conclusion, the use of neoadjuvant TK inhibitors in patients with resectable NSCLC is oncologically beneficial and feasible; however, more clinical trials are required to standardize the use of neoadjuvant TK inhibitors in patients with resectable NSCLC.

Targeting Anaplastic Lymphoma Kinase-Rearrangement in the Preoperative Period

Anaplastic lymphoma kinase, also known as CD246 or ALK receptor TK, is a characteristic 3-segment transmembrane receptor TK; extracellular domain, a transmembrane segment, and a receptor kinase segment.[43] The expression of the ALK receptor, which is necessary for the development of the nervous system, is high during neurodevelopment in the natal period and less in the postnatal stage.[43] That transmembrane protein is encoded by the ALK gene located on chromosome 2.[43] Three types of mutations occur in that gene: point mutation, amplification, and rearrangement.[43] The ALK/EML4 rearrangements induce important carcinogenic effects such as enhancing cell proliferation and triggering cell survival by generating an oncogenic receptor kinase.[43] In addition, the ALK rearrangement was found in 7% of NSCLC patients in 2007,

Table 3. Gefitinib in Resectable-Stage Neoadjuvant Therapy

First Author	Year	Number of Patients	Stages	Targeted Therapy Agent	Reference
Zhang	2021	33	Resectable stage II-IIIA non-small cell lung cancer	Gefinitib	42
Lara-Guerra	2009	36	Stage I non-small cell lung cancer	Gefinitib	40
Rizvi	2011	50	Stage I or II NSCLC	Gefinitib	41

NSCLC, non-small cell lung cancer.

Table 4. Crizotinib in resectable-stage neoadjuvant therapy

First Author	Year	Number of Patients	Stage	Agent	Reference
Zhang	2019	11	locally advanced NSCLC (resectable)	Crizotinib	47

NSCLC, non-small cell lung cancer.

making it the first described ALK mutation in NSCLC.[44] The oncogenic effects and incidence of ALK rearrangements have made it a therapeutic target.[43-45] Crizotinib as an orally administered small molecular inhibitor with a molecular weight of 450.34 Dalton has been approved by the FDA for the treatment of advanced ALK-positive NSCLC.[45]

Initially, that multitargeted small molecule inhibitor was developed for inhibiting mesenchymal–epithelial transition growth factor (c-MET).[45] Subsequently, it was used as a selective and potent inhibitor of ALK receptor kinase.[45] The mechanism of action of crizotinib mainly consists of targeting the ALK receptor kinase, inhibiting its phosphorylation, thereby inhibiting the signaling pathways that trigger the proliferation and cell survival of tumor cells.[45] Solomon et al[46] conducted an open-label, phase 3 clinical trial with 343 patients with advanced ALK-positive nonsquamous NSCLC. They reported that progression-free survival and objective response rate were significantly improved with crizotinib, but there was no significant change in OS.[46] Generally, crizotinib was used in the treatment of advanced and metastatic NSCLC. There is only 1 study for its use in a neoadjuvant setting (Table 4).

Zhang et al[47] conducted a study of 11 operable patients with ALK-positive pathologically confirmed N2 NSCLC who received neoadjuvant crizotinib. As a result of this study, authors observed a partial response rate of 91%, and a pathological complete response rate was reported as 18.2%. In addition, they reported pathological N downstaging in 3 patients (27.3%).[47] However, 1 patient had a grade 4 hepatotoxicity, but the patient recovered and continued to receive neoadjuvant crizotinib after a 1-week break.[47]

Consequently, the use of neoadjuvant crizotinib in ALK-positive patients might improve therapeutic response. Nevertheless, more studies are required for the feasibility and safety of neoadjuvant therapy for the therapeutic promise of crizotinib or other ALK inhibitors.

Immunotherapies in the Preoperative Period

Immunotherapies are one of the most emphasized topics in oncological medicine. It depends on stimulating immune cells to respond to tumor cells. Normal immune mechanisms are programmed to destroy pathogens; however, the altered tumor microenvironment of cancer manipulates immune cells in favor of the tumor using immune checkpoint death ligands such as PD1/PD-L and release factors that affect dendritic cells and macrophages. Although the concept of immunotherapy initially tried to evoke responses by mimicking cytokines, today it is more focused on inhibiting immune checkpoints.[48,49]

Although the first immunotherapy concept trials were conducted with agents such as nonspecific BCG and thymosin before the nineties, they did not have any survival advantage. In the 90s, partial treatment response was reported in mediators such as IL2.[49,50] Subsequently, the era of immune checkpoint inhibitors started. The CA209-003 study showed an estimated 5-year OS rate of 16% in patients with advanced NSCLC receiving the immune checkpoint inhibitor nivolumab, which is promising for the advanced stage. Another immune checkpoint inhibitor is pembrolizumab, which was used in patients with advanced NSCLC who had previously received treatment, and the 5-year OS rate was reported as 23.2%.[51]

After the immunotherapies benefits for patients with advanced lung cancer are proven, the thoracic oncology world has been focusing on the neoadjuvant immunotherapy approaches. For this purpose, various research projects are ongoing. The NCT02927301 is one of the largest neoadjuvant immunotherapy projects using atezolizumab, a neoadjuvant immune checkpoint inhibitor, and they reported a complete response rate of 5.2% and a major pathologic response of 19.5% in their report with 90 patients who underwent surgery.[52] In NADIM, nivolizumab + paclitaxel + carboplatin-containing neoadjuvant trial, there was a major pathological response in 85.4% of the patients and, more importantly, a complete response in 71.4% of the patients after neoadjuvant immunotherapy plus chemotherapy.[53] In another immunochemotherapy trial, NCT02716038, it was found that immunotherapy + chemotherapy was more effective than pure chemotherapy in terms of major pathological response.[54] In the NEOSTAR randomized controlled trial, it was reported that the inclusion of nivolumab in chemotherapy increased the neoadjuvant efficacy.[55] At the dawn of immunotherapies, there are some challenges to overcome with neoadjuvant immunotherapy. First, each tumor must have its own immune environment and the profiles of this environment must be fully determined. It should be determined which immunotherapy can be effective for which environment and it should be determined that it can be more effective when combined with which chemotherapy.

Future Perspectives

Despite significant advances in the treatment of NSCLC, the OS rate for NSCLC is not as high as expected. Although surgery is the optimal option for NSCLC treatment, a significant number of patients who underwent surgery cannot be cured completely. The recurrence rate after surgery could be as high as 82% for 1 year. Micrometastases of the tumor mostly play a role in postoperative recurrences. Better preoperative treatment is required to overcome micrometastases and reduce the recurrence rate. Preoperative chemotherapy and chemoradiotherapy could eliminate micrometastases and reduce recurrences in a fraction of patients. However, more selective preoperative treatment agents are required for heterogeneous genotype NSCLC in the era of case-based therapies.

Targeted therapies, which are mostly used in advanced stages, provide the opportunity for case-based treatment when used in the preoperative period. The targeted therapies are oncologically beneficial, feasible, and safe. However, comprehensive studies are required to elucidate all aspects of neoadjuvant targeted therapies and to determine the preoperative effects of newly used targeted therapy approaches such as BRAF, ROS1, and RET inhibitors, which might be effective in various and well-selected groups.

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