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REVIEW

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Update on adjuvant therapy in completely resected NSCLC patients

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Abstract

In patients with completely resected non-small cell lung cancer (NSCLC), postoperative adjuvant chemotherapy has been associated with improvement in survival by minimizing the risk of recurrence. For years, systemic chemotherapy including platinum based regimen has been a mainstay treatment modality of adjuvant treatment after complete resection. ADAURA study showed that among completely resected IB to IIIA NSCLC, disease-free survival was significantly better in patients under adjuvant osimertinib than a placebo group. After the advent of a variety of new treatment regimens, such as third generation TKI and immunotherapy, the landscape of postoperative adjuvant treatment has been changing. In this review, we discuss some key issues regarding choice of adjuvant treatment after complete resection in NSCLC, and provide further updates on recent advances in treatment modalities.

KEYWORDS

adjuvant, biomarker, immunotherapy, non-small cell lung cancer, osimertinib

INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for 85% of all newly diagnosed lung cancer cases. Among NSCLC, about 20% of patients are diagnosed with stages I and II, and 30% with stage III.[1,2] In NSCLC, stages I–IIIA are considered as early stage cancer in which the mainstay treatment is surgery.[3] In order to minimize the chance of postoperative recurrence and eradicate residual diseases, adjuvant treatment has been recommended for the patients. In patients with completely resected NSCLC, postoperative adjuvant chemotherapy has been associated with better overall survival (OS) in patients with early-stage disease.[4–7] The main objectives of postoperative adjuvant treatment are to minimize the risk of recurrence and ultimately improve survival in patients with NSCLC. For years, systemic chemotherapy including platinum-based regimen has been a mainstay treatment modality of adjuvant treatment after complete resection.[8–10]

After the advent of variety of new treatment regimens, such as third-generation tyrosine kinase inhibitors (TKIs) and immunotherapy, the landscape of postoperative adjuvant treatment has been changing. The ADAURA study showed that among completely resected stage IB to IIIA NSCLC, disease-free survival (DFS) was significantly longer among patients under adjuvant osimertinib than the placebo group.[11] Current NCCN guidelines recommend the use of osimertinib for patients with completely resected stage IB–IIIA epidermal growth factor receptor (EGFR) mutation-positive NSCLC who have received prior adjuvant chemotherapy, or are unable to undergo platinum-based chemotherapy.[12] After careful consideration of the postoperative pathological findings, initial tumor burden, mutation profiles and programmed death-ligand 1 (PD-L1) uptake, clinicians should choose the optimal adjuvant treatment modality amongst ever diverse modalities after complete resection.

In this review, we discuss some key issues regarding choice of adjuvant treatment after complete resection in patients with NSCLC, and provide further updates on recent advent in treatment modalities.

METHOD

Search strategy

Following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines,[13] literature on adjuvant treatment in resectable NSCLC was searched online. The National Center for Biotechnology Information (NCBI) PubMed, Cochrane Library, Google Scholar, and EMBASE were searched. Articles published in English between January 2016 and June 2021 were included. Combinations of the following terms were searched online; "NSCLC", "non-small cell lung", "stage IB", "stage II", "stage III", "stage IIIA", "stage IIIB", "locally advanced", "resectable", "resected", "adjuvant", "chemotherapy", "postoperative", "immunotherapy", "radiation", "biomarker", "prognosis", "relapse", and "recurrence".

UPDATE ON BIOMARKERS PREDICTING PROGNOSIS IN COMPLETELY RESECTED NSCLC

It is well known that clinical factors such as pathological subtypes, lymphovascular invasion, and large tumor burden are associated with poor progression-free survival (PFS) in completely resected NSCLC patients.[14,15] The current approach in detecting postoperative tumor recurrence after complete resection is focused on finding macroscopic relapse by radiological examination such as computed tomography (CT). The radiological findings can sometimes be inconclusive due to postoperative normal tissue changes,[16] so more sensitive means of detecting recurrence in patients who undergo complete resection is necessary. During the last few years, technological advances in genetic and molecular fields have enabled more diverse approaches in predicting locoregional and distant recurrence, and the addition of new treatment modalities such as third-generation TKI and immunotherapy requires more studies on immunogenomic signatures to allow the selection of more appropriate treatment modalities.

The use of plasma circulating tumor DNA (ctDNA) for predicting postoperative recurrence is being studied for the detection of molecular residual disease. CtDNA are DNA fragments in the blood which consist of tumor-specific somatic alterations, and can be detected without causing much discomfort to patients.[16] In a study including 77 NSCLC patients, preoperative ctDNA-positivity was predictive of recurrence-free survival (RFS) and OS in NSCLC patients who underwent complete resection. Furthermore, postoperative detection of ctDNA is likely to be associated with early relapse.[16] Postoperative circulating tumor cells as well as tissue AXL overexpression are also considered as potential prognostic biomarkers in patients who undergo lung adenocarcinoma resection.[17] The CAncer personalized profiling by deep sequencing (CAPP-seq) technique has been developed to detect ctDNA-derived somatic mutations,[18] and a personalized, tumor-informed assay such as Signatera, optimized to detect ctDNA for molecular residual disease detection and monitoring recurrence is also being used in clinical settings.

A meta-analysis including 15 studies showed that PD-L1 expression was predictive of shorter PFS and OS in an early stage resected NSCLC population, of which a significant proportion of stage III cancer patients were present.[19] Tumoral PD-L1 expression in combination with neutrophil-to-lymphocyte ratio (NLR) has been shown to be independently associated with RFS in a retrospective analysis of 83 patients who underwent complete resection of stage I squamous cell carcinoma of the lung.[20] Serial measurements of tumor markers such as cytokeratin 19 fragment (CYFRA 21-1) and human epididymis protein 4 (HE4) have shown modest sensitivity in detecting relapse after complete resection; however, the specificity was low.[21]

Driver mutations have been studied for their association with postoperative prognosis. Anaplastic lymphoma kinase (ALK) rearrangement was found to be associated with poor DFS and frequent regional lymph node metastasis in patients with completely resected IA adenocarcinoma.[22] C-MET protein overexpression from tissue samples was also studied, showing correlations with OS and potential values as a biomarker in patients undergoing adjuvant treatment.[23] Different combinations of gene signatures from tumor tissues, which are detectable by various platforms, have also been studied for their value as a biomarker predicting efficacy of adjuvant treatment.[24] Next-generation sequencing (NGS) allows simultaneous detection of various mutated genes. A study including surgical specimens from 230 patients with resected stage I–II lung adenocarcinoma showed that NGS could be a potential biomarker for predicting recurrence. After median follow-up time of 49 months, recurrence was observed in 64 patients (27.8%). CTNNB1 mutation and fusion genes (ALK, ROS1, RET) detected from targeted NGS were negative prognostic factors for recurrence. The application of targeted NGS as a predictor for recurrence was found to be affected by a number of factors such as variety of genes which can be detected by the tests, and it would provide important genetic data which may relate to postoperative recurrence.[25] In other study, it was shown that detection of various mutated genes using NGS can help predict brain metastasis and prognosis after complete resection.[26] Nevertheless, the potential biomarkers require prospective studies for use in real-clinical settings.

An analysis of 91 paired resected stage II/III NSCLC along with matching normal tissues revealed that higher neoantigen load (>2 neoantigens/Mb) was associated with better DFS in squamous cell carcinoma patients ($p = 0.021$).[27] A 14-gene expression assay using quantitative PCR, performed on paraffin-embedded tissue samples, assisted in identifying subjects with localized nonsquamous NSCLC at higher risk of poor outcome after resection.[28]

Immune cell signatures are also assessed for their value as potential biomarkers predicting prognosis after complete resection. A recent study included the specimens obtained from 384 NSCLC patients who underwent complete resection evaluated the predictive value of immunohistochemical

assays of CD47 and CD68. High expression of CD47 was associated with poor RFS, while showing correlation with large tumor size and poor TNM staging.[29] An analysis of gene expression data of 292 patients with early stage cancer (IA/IB) showed that levels of macrophages and plasma cells along with T regs and non-TregCD4+ T cells in tumors can assist in finding patients at a higher risk of recurrence.[30]

Aside from the aforementioned potential biomarkers, prompt detection of PD-L1 expression and target mutation such as *EGFR* mutation became ever more important. Not just for a value as a biomarker, but because targeted therapies such as osimertinib can be used as adjuvant treatment and a combination treatment including immunotherapy can also be considered as an adjuvant treatment in the near future.[11]

EGFR MUTATION

EGFR mutation is associated with favorable local control and prognosis in NSCLC; however, patients with these mutations are at an increased risk of distant relapse.[31] An important question is whether conventional chemotherapy or EGFR TKI would be more appropriate as adjuvant therapy after complete resection in NSCLC patients with *EGFR* mutation.

A phase 3 ADJUVANT/CTONG1104 study has shown a significant increase in DFS among stage II–IIIA patients with EGFR exon 19 or 21 mutation who received adjuvant gefitinib for up to 24 months, in comparison with adjuvant vinorelbine plus cisplatin. Median DFS of the gefitinib group was 30.8 months, while reducing disease recurrence or mortality when compared to the vinorelbine plus cisplatin group.[32] Another phase 2 trial also showed improvement in two-year DFS and safety in *EGFR*-mutant stage IIIA NSCLC after adjuvant erlotinib compared with conventional chemotherapy.[33] In stage III–pN2 lung adenocarcinoma, adjuvant TKI showed significant efficacy in improving OS, and showed superior outcome when compared to systemic conventional chemotherapy.[34] Adjuvant chemotherapy is not associated with dramatic survival benefit in patients with stages IB NSCLC after complete resection. In addition, a phase II trial evaluating efficacy of icotinib as an adjuvant treatment in patients with fully resected stage IB NSCLC with *EGFR* mutation is ongoing (NCT02264210).[35]

Osimertinib is possibly a highly effective treatment modality as an adjuvant treatment in completely resected IIIA NSCLC. The ADAURA study revealed that DFS was significantly longer for patients under osimertinib when compared with the placebo group.[11] Survival data is immature, and whether superior outcome in PFS would result in longer survival needs confirmation, but it is undeniable that use of osimertinib in the completely resected NSCLC patient with *EGFR* mutation would be a promising treatment modality. TKI monotherapy is a potentially reliable option in the adjuvant treatment of completely resected NSCLC with *EGFR* mutation.

Furthermore, the *EGFR* mutation positive subgroups deserve distinctive clinical attention, as they show a different clinical course when compared to their *EGFR* wild-type counterparts. Thus, prognostic factors within this group should be studied separately. Among 288 completely resected stage III pathological N2 NSCLC patients with *EGFR* mutation, pretreatment bulky/multilevel N2 and pathological extranodal extension were associated with locoregional recurrence.[36] The authors further discussed that in comparison to wild-type patients, the majority of *EGFR*-mutant patients had more unforeseen N2 which were confirmed after the resection.

IMMUNOTHERAPY

Several trials are ongoing regarding the use of immunotherapy as an adjuvant treatment after complete resection (Table 1). Most of the ongoing trials regarding efficacy of immunotherapy include patients who completed usual chemotherapy after the complete resection.

While immune checkpoint inhibitor (ICI) monotherapy does not show any major breakthroughs, a synergistic effect from combination treatment may provide an additional option. An attempt to use combination of immunotherapy and platinum doublet chemotherapy as neoadjuvant or adjuvant therapy is ongoing. Keynote-671, a phase III, randomized, double-blind trial comparing platinum doublet and a combination treatment in patients with resectable stage II, IIIA, and IIIB is expected to show primary results in a few years.[37] The phase III ALCHEMIST trial (NCT04267848) evaluates the efficacy of additional pembrolizumab to usual chemotherapy in comparison to usual chemotherapy alone in completely resected NSCLC patients. Patients receive 17 cycles of pembrolizumab in the absence of disease progression or severe toxicity.[38] A trial evaluating efficacy of nivolumab in patients with stage IB-IIIA NSCLC who underwent surgery and chemotherapy is also ongoing (NCT02595944).[39] Another phase III, multicenter, open-label, randomized study (NCT02486718) in a similar study design compares the safety and efficacy of 16 cycles of atezolizumab compared with supportive care in patients with stage IB–IIIA NSCLC who underwent resection and adjuvant chemotherapy.[40] The primary results of IMpower010, a phase III study of atezolizumab versus best supportive care, showed benefit in DFS after adjuvant chemotherapy in patients with resected stage II–IIIA NSCLC. The clinical benefit was more pronounced in the subgroup with PD-L1 TC > 1%.[41] A phase II study with cisplatin plus vinorelbine combined with atezolizumab as an adjuvant therapy for stage II–IIIA with completely resected NSCLC with *EGFR* mutation is ongoing.[42] The results of ongoing studies will contribute to acquiring more options in the patient groups.

Durvalumab is fully human IgG1 monoclonal antibody that blocks the PD-L1-PD-1 interaction. Based on the results of the PACIFIC trial, durvalumab is used as adjuvant treatment after definitive CCRT on unresectable stage III

TABLE 1 Notable ongoing trials on adjuvant treatment after complete resection in patients with NSCLC

Treatment numbers	Study patients	Study model	Details
MK-3475-671/Keynote-671 (NCT03425643).[37]	Resectable stage II, IIIA, and resectable IIIB (T3-4N2) NSCLC	A phase III, randomized, double-blind trial comparing platinum doublet and a combination treatment	Neoadjuvant pembrolizumab in combination with neoadjuvant chemotherapy, followed by surgery and adjuvant pembrolizumab (vs. placebo). The efficacy of the treatment was compared with the placebo. Primary outcomes: 1) event free survival (EFS) and 2) overall survival (OS).
ALCHEMIST trial (NCT04267848).[38]	Stage IB, II, or IIIA NSCLC that has been removed by surgery	A randomized phase III trial	The study evaluates the efficacy of additional pembrolizumab to usual chemotherapy in comparison to usual chemotherapy alone.
ALCHEMIST Treatment Trial (NCT02595944).[39]	Patients with stage IB-IIIA NSCLC	A randomized phase III trial	The study evaluates the efficacy of nivolumab after surgery and chemotherapy in patients with stage IB–IIIA. Primary outcomes: OS and/or disease-free survival (DFS)
IMpower010 (NCT02486718).[40]	Patients with stage IB–IIIA NSCLC	A phase III, multicenter, open-label, randomized study	In patients with stage IB-IIIA NSCLC following resection and adjuvant chemotherapy, the study compares the efficacy and safety of 16 cycles of atezolizumab treatment compared with supportive care Primary outcomes: DFS
West Japan Oncology Group 11 719 L/ADJUST study.[42]	Stage II–IIIA with completely resected NSCLC with EGFR mutation	A multicenter, single-arm prospective, phase II study	In patients with completely resected NSCLC with *EGFR* mutation, the efficacy of the combination regimen (cisplatin plus vinorelbine combined with atezolizumab) as adjuvant therapy was evaluated. Primary outcome: 2-year DFS

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

cancer.[43,44] However, the NCCN guidelines do not recommend the use of durvalumab monotherapy as a single adjuvant treatment for patients who have had surgical resection.[12] Ongoing trials to evaluate the impact of durvalumab as an adjuvant treatment include patients who underwent complete resection and usual platinum-based chemotherapy. In an open label, multi-institutional, single arm phase II trial (NCT03871153), the study patients undergo induction treatment of carboplatin, paclitaxel, durvalumab and radiation, and undergo surgical resection if they remain surgical candidates after the induction. Patients who undergo surgical resection will receive adjuvant durvalumab treatment for six cycles.[45]

SIGNIFICANCE OF NODAL STAGES IN PROGNOSIS AFTER COMPLETE RESECTION

Among the patients with NSCLC, stage III cancer accounts for 30%.[1] The overall median PFS and median OS are 12.5 and 34.9 months, respectively. Among stage III cancer patients, about 21.0% undergo curative resection,[46] and stage IIIA cancer is more likely to be resectable than IIIB and IIIC. However, 5-year OS of stage IIIA cancer is 20%–35% with a high chance of relapse,[1,47] and nodal stage is important for predicting prognosis and selection of adjuvant treatment modalities.

The current nodal staging does not fully describe all the heterogeneous disease burden in mediastinal lymph nodes. In comparison with minimal N2 disease which is not seen before surgical resection, more evident clinical N2 stage shows a relatively worse prognosis in patients with NSCLC undergoing resection.[48] Patients with stage IIIA disease with N2 nodal involvement have an overall 5-year survival rate of 10%–15%, and in bulky N2 subgroups specifically, OS is decreased. Furthermore, patients with bulky N2 are not likely to initially undergo complete resection. It is evident that prognosis is likely to be unfavorable if burdens of the involved N2 nodes are heavier.

Furthermore, within the same nodal stage, patients with multiple lymph node involvement are more likely to have a higher possibility of relapse after complete resection when compared to patients with single lymph node involvement. A retrospective analysis of 1989 patients with NSCLC who underwent complete resection by lobectomy or pneumonectomy showed that single node metastasis was independently associated with better OS when compared to multiple node metastasis in pathologically proven N1 diseases which was classified according to the eighth edition of TNM.[49] Andre et al. analyzed a multicenter cohort in which 702 patients with resected stage IIIA–N2 NSCLC were included. The study identified that involvement of multiple lymph node levels, pathologically proven T3 to T4 stage, and no preoperative chemotherapy were prognostic factors.[48] In addition,

a study showed that radiotherapy after complete resection was more effective in patients with single N2 station involvement.[50]

In order to implement more precise risk stratification in early NSCLC, an attempt to add molecular prognostic classifier to TNM classification was made. Based on data of 321 patients with stage I–III NSCLC, a 14-gene molecular prognostic classifier was integrated into the eighth edition of the TNM staging (TNMB, B stands for biology). When compared with the eighth edition of the TNM system, the TNMB staging system better showed high-risk patients, and better predicted differences in survival.[51]

ROLE OF RADIOTHERAPY IN PATIENTS WHO UNDERGO COMPLETE RESECTION

Postoperative radiotherapy (PORT) is not routinely recommended for patients with stage I and II cancer, but rather for patients with completely resected stage III cancer. NCCN guidelines recommends postoperative RT if patients who underwent complete resection show positive resection margins.[12,52–54] Whether patients should undergo concurrent or sequential radiotherapy does not have a definite answer. Francis et al. showed that patients with NSCLC who undergo R0 resection and have pN2 disease have improved outcomes when they received adjuvant chemotherapy before, rather than concurrently with, radiotherapy. In patients with positive margins after surgery (R1-2), there was little evidence for association between treatment sequencing and survival.[55]

In patients with N0-1 disease, chest wall lesions with T3 invasion-T4 extension, patients who initially underwent surgery and show positive surgical margins may receive either 1) sequential or concurrent chemoradiation; or 2) re-resection and chemotherapy. The NCCN guideline recommends in favor of concurrent chemoradiation in positive margin cases, but sequential treatment can also be considered for patients who are unable to tolerate concurrent treatment.[12,54]

However, not all stage III patients who undergo complete resection benefit from PORT. In 576 patients with IIIA–N2 NSCLC who underwent resection, PORT was not associated with improvement in OS and DFS, but in patients with single N2 station involvement, PORT was beneficial.[50] Effects of PORT using modern techniques such as 3D-CRT and IMRT on survival and safety in patients with pIIIA-N2 NSCLC after complete resection and adjuvant chemotherapy was evaluated in a randomized clinical trial (NCT00880971). Patients were randomized into the PORT arm (n = 202) or the observation arm (n = 192). The 3-year DFS rates were 40.5% in the PORT arm and 32.7% in the observation arm (median, 22.1 vs. 18.6 months); however, there was no statistically significant difference in DFS. The study showed that PORT has a possibility of improving DFS and reducing the chance of locoregional relapse, while showing relatively tolerable safety profiles. It should be noted that the study was a single-center study, not properly stratified. Among the patients, 21.7% of the patients in the PORT arm refused PORT, and 5.6% in the observation arm actually received PORT.[56] LungArt trial (NCT00410683) is the randomized study evaluating PORT after complete resection in which patients received perioperative chemotherapy. The study showed that PORT (54 Gy/27–30 fractions) was associated with a nonstatistically significant 15% increase in DFS among the stage IIIAN2 patients when compared with patients who did not undergo PORT.[57] The recent studies show that effect of radiation is not definite in stage III N2 disease, possibly due to the heterogeneity in terms of disease burden which exist in the population. More studies are necessary to find the optimal treatment candidates.

OTHER ONGOING TRIALS

An ongoing phase II of alectinib, entrectinib, or vemurafenib/cobimetinib therapy before surgery in patients with non-metastatic NSCLC with ALK, ROS1, NTRK, or BRAF V600E will evaluate the potential efficacy of variety of targeted therapies for use as both neoadjuvant and adjuvant treatment. Before surgery, patients with *ALK* mutations receive the alectinib, those with ROS1 or NTRK gene mutations receive entrectinib, and patients with *BRAF* gene mutations receive vemurafenib and cobimetinib before surgery. If benefits of the neoadjuvant treatment are present, patients may continue to take it after surgery.[58] In another phase II, open-label, single-arm, multicenter clinical trial (ALNEO study, EUDRACT number 2020–003432-25), patients with potentially resectable stage III ALK positive NSCLC will receive oral alectinib both as the neoadjuvant and adjuvant treatment. After definitive surgery, patients can receive alectinib 600 mg twice for 96 weeks.[59]

CONCLUSIONS

Adjuvant treatment in completely resected NSCLC patients mainly include platinum-based chemotherapy. However, due to advents in treatment modalities, EGFR-TKI and combination treatment including immunotherapy are also being considered for alternative treatment. Studies on biomarkers predicting relapse and results of ongoing trials will contribute to the management of patients with resectable NSCLC.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article. The authors have stated that they have no conflicts of interest.

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