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Review Article

Systemic Adjuvant Therapy in Non-Small Cell Lung Cancer (NSCLC)

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Abstract

Lung cancer is still a major health problem. In this context, surgical treatment is very important but unfortunately only about a quarter of the patients diagnosed with lung cancer are operable and the overall 5-year survival is unsatisfactory Adjuvant therapies have been investigated in randomized clinical trials to minimize the risk of disease recurrence after surgery. The first meta-analysis published in 1995 about adjuvant systemic therapy brought modest but objective evidence on its benefits. The consolidation of surgical results through systemic adjuvant therapy is important and addressed in this article that describes the main clinical trials that imposed adjuvant chemotherapy as standard of care. New treatments introduced into the therapeutic arsenal of lung cancer, such as targeted therapy and immunotherapy, recently demonstrated a role in the adjuvant settings and were highlighted at the end of this article.

Keywords: *Non-Small Cell Lung Cancer; Early Stage; Systemic Therapy*

Introduction

Lung cancer is the leading cause of cancer death worldwide. The survival rate ranged, unfortunately, from 30 to 60% even with the early diagnosis of the disease. The main histological types of lung cancer are represented by the non-small cell lung cancer (NSCLC) that makes about 87% of cases and the small cell lung cancer. 2012 data from the Agency for Research in Cancer shows that lung cancer in Europe had an incidence of 254532 (rate 59,1/100.000) and a mortality of 290705 (rate 68,3/100.000) [1]. 2016 data from the American Cancer Society estimates that in the United States there were about 224,390 new cases of lung cancer (117,920 in men and 106,470 in women) and about 158,080 deaths from lung cancer (85,920 in men and 72,160 in women).

Patients with stage I, II and certain stage III NSCLC are considered eligible for curative radical resection. Adjuvant therapies have been investigated in randomized clinical trials to overcome the high risk of disease recurrence after surgery. Many trials are evaluating the utility of the targeted agents as adjuvant therapy based on the treatment benefit observed in patients with advanced-stage disease and driver genetic alterations in their tumors. Similarly, clinical benefit observed with checkpoint inhibitors has prompted assessment of these drugs, like adjuvant or consolidation therapy, for patients with operable stage NSCLC.

We will present in this article the systemic therapy in NSCLC operable stages.

This therapy named adjuvant therapy was demonstrated in clinical trials that can determine an increase overall survival. This article is an overview of best evidence of efficacy of adjuvant chemotherapy. Also, we present a new trend in adjuvant therapy considering some new data from clinical trials with immunotherapeutic agents and target therapy.

The radiotherapy does not yet have a very clear role in the strategy of adjuvant therapy and for that reason we will only present our expertise as medical oncologist.

Adjuvant chemotherapy

The first evidence of the beneficial effect of adjuvant chemotherapy was the results of a meta-analysis published in British Medical Journal (BMJ) in 1995 [1]. This meta-analysis included 9387 patients from 52 published or unpublished randomized clinical trials. The main objective of this meta-analysis was to determine the overall survival. At that time progression free survival was not a factor to watch. The results for the cisplatin containing chemotherapy regimens were favorable in all comparisons and reached conventional levels of significance when used with radical radiotherapy and supportive care. A comparison between patients receiving surgery followed by chemotherapy versus surgery alone resulted in a hazard ratio of 0.87 that meant a 13% reduction of risk of death and an absolute benefit of 5% at five years.

Trials comparing radical radiotherapy with chemotherapy plus radical radiotherapy gave comparable results to those where chemotherapy was associated or not to surgery (hazard ratio of 0.87 that means 13% reduction in the risk of death and an absolute benefit of survival of 4% at two years). Also, patients treated with chemotherapy and supportive care had a better survival compared to those treated with supportive care only (hazard ratio 0.73 that means 27% reduction in the risk of death and a 10% improvement in survival at one year). These findings meant that radiotherapy associated with chemotherapy do not improve the results when compared with chemotherapy alone.

In the early 2000 Scagliotti and colleagues completed a randomized trial that compared patients who received mitomycin C (8 mg/m^2 on day 1), vindesine (3 mg/m^2 on days 1 and 8), and cisplatin (100 mg/m^2 on day 1) every 3 weeks for three cycles (MVP group; n = 606) with patients without treatment (control group; n = 603) after complete resection. This trial failed to prospectively confirm a statistically significant role for the adjuvant chemotherapy in completely resected NSCL [2].

National Comprehensive Cancer Network (NCCN) Guidelines for NSCLC from 2018 recommend adjuvant chemotherapy {with or without radiotherapy for operable NSCLC stages starting with stage IB (high-risk patients in stage IB)} to IIIA [3]. A Cochrane analysis published online in March 2015 looked at the role of adjuvant therapy for NSCLC by reviewing two meta-analyses. They reviewed several randomized controlled trials comparing: a) surgery versus surgery plus adjuvant chemotherapy; and b) surgery plus radiotherapy versus surgery plus radiotherapy plus adjuvant chemotherapy. The authors searched for relevant clinical trials published until December 2013. These studies brought together trial data from all over the world with 26 trials (34 trial comparisons) and 8447 patients in the first meta-analysis (surgery versus surgery plus adjuvant chemotherapy); and 12 trials (13 trial comparisons) and 2660 patients in the second meta-analysis (surgery plus radiotherapy versus surgery plus radiotherapy plus adjuvant chemotherapy). All trials were carried out between 1979 and 2003. The results revealed that people with NSCLC who had surgery followed by chemotherapy (with or without radiotherapy) lived longer than those who had surgery without chemotherapy (with or without radiotherapy). In both meta-analyses, there was little variation in the effect of chemotherapy, other trial characteristics, or type of patients included in the trials. Authors concluded that results from 47 trial comparisons that included 11,107 patients demonstrate the clear benefit of adjuvant chemotherapy for these patients [4].

International Adjuvant Lung Trial (IALT) was another trial aimed at finding a benefit in survival for patients with resected stage I, II or IIIA NSCLC who have received adjuvant cisplatin-based chemotherapy compared to just observation The primary endpoint was OS and the secondary endpoint consisted of disease free survival (DFS). Other objectives were the incidence of second primary cancers and adverse effects. A total of 1867 patient were randomized to either receive chemotherapy (n = 932) or observation (n = 935). Patients in the

chemotherapy arm were treated with one of 4 agents different than cisplatin: etoposide, vinorelbine, vindesine, or vinblastine. Patients with pathologic stage N1 or N2 disease could have received radiotherapy after completion of chemotherapy regardless of them being assigned to treatment or to observation. The chemotherapy arm had a better median OS (HR, 0.86; P < .03) and a higher 5-year OS rate (40.5% vs 44.5%, respectively) compared with the observation arm. DFS was also significantly higher in the chemotherapy group (HR, 0.83; P < .003). This study was an argument in favor of using adjuvant chemotherapy after surgery in resected NSCLC.

National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) published a phase III randomized trial to determine the benefit of adjuvant chemotherapy in patients with resected stage IB or stage II (T2N0, T1N1, or T2N1) NSCLC. The study was designed to detect a 10% improvement in OS. A number of 482 patients were randomized to four cycles of adjuvant chemotherapy with cisplatin and vinorelbine or to observation. The median duration of follow-up was 5.3 years for the observation group and 5.1 years for the chemotherapy group. Patients received a median of three cycles of treatment. Recurrence was significantly decreased in the chemotherapy group (HR, 0.60; P < .001) and median OS was significantly prolonged in the chemotherapy group compared with the observation arm (95 months vs 73 months, respectively; HR, 0.69; P = .04). The survival was studied by the disease stages. The results of this study revealed no statistically significant benefit associated with chemotherapy in patients with stage IB NSCLC (P = .79) but a significant one in patients with stage II NSCLC. A long-term follow-up data accrued during a median of 9.3 years that was published in 2010 confirmed the initial results of the trial, namely a benefit from adjuvant chemotherapy, (HR, 0.78; P = .04) and reported a prolongation of disease-specific survival (HR, 0.73; P = .03). A correlation between benefit from chemotherapy and stage of the disease was reported as well. Patients with stage II disease who received chemotherapy demonstrated a significant OS benefit (HR, 0.68; P = .01) compared with their counterparts from the observation arm. Patients with stage IB disease showed no OS benefit versus the subgroup of patients with stage IB disease in the observation arm (HR, 1.03; P = .87). The analysis of patients with stage IB disease found that patients with tumors >4 cm benefited from adjuvant chemotherapy compared with observation, but the level of benefit was not statistically significant (HR, 0.66; 95% CI, 0.39-1.14; P = .133).

Adjuvant Navelbine International Trialist Association (ANITA) was a European multinational study of adjuvant chemotherapy consisting in vinorelbine plus cisplatin versus observation. The patients enrolled were in stage IB-IIIA NSCLC and underwent a total resection of the tumor. A number of 840 patients received chemotherapy (n = 407) or observation (n = 433) after randomization. Radiotherapy was permitted by the local protocols. Median duration for follow-up was 76 months. Overall median survival was 65.7 months for the patients in the chemotherapy arm and 43.7 months for the patients in the observation arm (HR, 0.80; P = .017). OS benefit at 5 years with the use of chemotherapy was 8.6% at 5 years and 8.4% at 7 years. The subgroup analysis of patients with stage IB revealed no benefit from chemotherapy, with a 5-year OS rate of 62% in the chemotherapy group versus 64.5% in the observation group (HR, 1.10; CI, 0.76 - 1.57). A significant benefit for patients randomized to chemotherapy versus those randomized to observation, with a 5-year OS rate of 51% versus 39%, respectively (HR, 0.71; CI, 0.49 - 1.03), was noticed in the patients with stage II disease. An important outcome was also seen in patients with stage IIIA in the chemotherapy arm who experienced a significant prolongation of survival, with a 5-year OS rate of 42% versus 26% in the observation group (HR, 0.69; CI, 0.53 - 0.90) (P = .07) [5,6].

Target therapy

Nowadays, small molecules, especially tyrosine kinase inhibitors (TKI) and monoclonal antibody, are largely used in advanced cancer and several clinical trials are trying to reveal the role of these compounds in the early stage of lung cancer.

Target therapy hes improved the results of treatment in NSCLC. However, the use of target therapy is not well defined for localized tumors with NSCLC histology and the results are inconclusive for wild type of Epidermal Growth Factor Receptor (EGFR). There are only a few studies with small number of patients enrolled and with many of them conducted in a single center for patients with localized NSCLC and EGFR mutation, reason why the level of evidence is small.

There are ongoing phase III trials comparing adjuvant tyrosine kinase inhibitor administration versus adjuvant chemotherapy. The

RADIANT study compared erlotinib in adjuvant settings versus placebo by enrolling 102 patients from the subgroup with EGFR mutated tumors in the arm treated with erlotinib and 59 patients in the placebo arm. The group treated with erlotinib included more patients in stage IB/IIA and less frequent adjuvant chemotherapy. PFS was better in the erlotinib arm (46 vs 28 months, P = 0.04) with no difference between arms in OS (P = 0.8). It was also noted that the proportion of patients with cerebral relapse was higher in the erlotinib arm (40%) than in the placebo arm (13%) [7].

Bevacizumab is one of the first drugs used in neoadjuvant settings. A phase III trial, ECOG 1505, tested the following chemotherapy options: cisplatin/vinorelbine, cisplatin/docetaxel, cisplatin/gemcitabine, and cisplatin/pemetrexed (for non-squamous histology only), with or without bevacizumab in patients with resected IB-IIIA NSCLC (the patients with stage IB disease must have had tumors measuring at least 4 cm). The primary endpoint was OS and the conclusion of this trial was that bevacizumab did not improve OS or DFS. E1505 chemotherapy subset analysis was really the biggest update on adjuvant treatment. All these regimens looked relatively equivalent, with pemetrexed being a good choice for toxicity reduction in some cases [8].

The ongoing JIPANG study is a randomized study comparing cisplatin (75 mg/m^2, day 1) and pemetrexed (500 mg/m^2, day 1) with cisplatin (80 mg/m^2, day 1) and vinorelbine (25 mg/m^2, days 1 and 8) for non-squamous NSCLC as a postoperative adjuvant chemotherapy. The results of this study hope to more clearly define the best chemotherapy regimen in adjuvant settings [9].

A study published in 2009 in the New England Journal of Medicine by Mok TS., *et al*. demonstrated the superiority of TKI gefitinib versus chemotherapy (carboplatin–paclitaxel) as first line therapy for pulmonary adenocarcinoma with EGFR mutation [10]. Positive result were also noted in the EURTAC study that enrolled European patients [11].

Anaplastic lymphoma kinase (ALK) translocations have been identified in a subset of adenocarcinomas and this abnormality is the product of an inverted translocation of EML4 gene located on chromosome 2p21 and the ALK gene located at 2p23 [12]. This gene modification has been detected in 7% of the lung adenocarcinomas [13]. Crizotinib small molecule is the first ALK inhibitor used in clinical practice for this translocation [14] but for the moment there is no evidence for its use as adjuvant therapy in NSCLC.

Kirsten rat sarcoma viral oncogene (KRAS) mutations are more common in lung adenocarcinomas than in other histological types of NSCLC and are more frequently found in patients with a smoking history (approximately 30%). KRAS mutations in lung cancer are found on codons 12, 13 and 61 and are mainly a GGT to TGT translocation that produce changes on glycine to cysteine amino acids [15]. RAS/RAF/MEK pathway is a potential therapeutic target in lung cancer but we only have evidence in the metastatic settings where the MEK1 inhibitor, selumetinib, combined with docetaxel demonstrated an improved PFS and a trend toward improved overall survival compared with docetaxel alone.

BRAF is a serine-threonine protein kinase that functions in the RAS/mitogen activated protein kinase signaling pathway. BRAF is downstream of KRAS and directly phosphorylates MEK. Subsequent phosphorylation of Extracellular Signal Regulated Kinase (ERK) is involved in proliferation and survival. Mitogen-activated protein (MAP) kinase is also known as extracellular signal regulated kinase (ERKs) and thought to act at an integration point for multiple biochemical signals because it is activated by a wide variety of extracellular signals [16].

Mutant BRAF proteins have increased kinase activity and are transforming *in vitro* [17]. BRAF mutations in NSCLC affect 1% to 3% of cancers [18,19]. BRAF mutations in NSCLC are seen almost exclusively in adenocarcinomas and are more common in current and former smokers. Patients with tumors harboring BRAF mutations have a distinct clinical profile compared with those with tumors bearing kinase domain mutations in EGFR [20]. These genetic aberrations are tested only for metastatic NSCLC like the anomalies described below.

HER2 (ERBB2) is a member of the ERBB family of receptor tyrosine kinases [21]. Activation of HER2 initiates the PI3K-AKT-mTOR and RAS-RAFMEK-ERK pathways, promoting cell survival and proliferation [22]. HER2 mutations are found in only 2% to 4% of NSCLC cases whereas HER2 overexpression or gene copy number gains are relatively common in NSCLC [23,24]. The most common mutation is an in-frame insertion in the exon 20. Clinically, HER2 mutations appear to be more common in women and in never-smokers with adenocarcinoma histology. The HER2 monoclonal antibody, trastuzumab and the TKI, lapatinib, have been evaluated in NSCLC patients. Trastuzumab combined with chemotherapy in unselected patients did not result in improved outcomes compared to historical controls treated with chemotherapy alone [25,26]. Similarly, single-agent lapatinib in an unselected population of patients with NSCLC demonstrated an overall response rate of only 1.3% [27]. Individual cases of response to HER2 targeted therapy in patients with HER2 mutations have been reported [28]. Also, partial responses to the pan-HER inhibitor, afatinib, in three pretreated patients with HER2 mutations were reported as well [30]. Angiogenesis plays an important role in tumor development and increased angiogenic signaling has been associated with poor prognosis in a number of malignancies including NSCLC [31].

Therapies targeting components of angiogenic signaling were developed over the past years. One of the best known is bevacizumab, a humanized monoclonal antibody with a high affinity for vascular endothelial growth factor (VEGF) that inhibits binding of VEGF to its receptors by attaching to the circulating VEGF [32]. In AVAiL study the combination of bevacizumab with cisplatin plus gemcitabine was superior in term of progression free survival than chemotherapy alone [33]. Mutations of DDR2, a tyrosine kinase, have been described in 4% of the lung squamous cell carcinomas. Dasatinib inhibits tyrosine kinases, including DDR2 and represents a new target that requires further investigation. More recently, gefitinib, a TKI of first generation, appears more effective in preventing recurrence after lung cancer surgery than chemotherapy that is considered standard of care. This conclusion was drawn by analyzing a phase III clinical trial in which patients with positive EGFR, stage II NSCLC, received gefitinib for about 10 months. No recurrence has been recorded compared to the group of patients who received chemotherapy (Wu., *et al*. ASCO 2017-Abstract 8500). In this respect authors considered that adjuvant gefitinib may be an important therapeutic option for stage II to IIIA NSCLC with an active EGFR mutation, and therefore routine EGFR testing in the early stage of lung cancer could be considered [34].

To the virtual ASCO meeting study ADAURA reveled very good results with osimertinib in adjuvant settings when compare with placebo. So, the disease-free survival at 2 years was doubled from 44% with placebo to 90% with osimertinib. The hazard ratio for the primary endpoint was 0.17. This study, in the opinion of some lieders in oncology will change lung cancer treatment [35].

Immunotherapy

The use of adjuvant immunotherapy is under investigation. Many positive trials have led the Food and Drug Administration (FDA) to approve several immunotherapeutic agents but for treatment of advanced NSCLC. Recently some studies revealed that immunotherapy could be beneficial and in adjuvant administration. Immunotherapy includes at this time vaccines therapy and immune checkpoint modulation.

The glycoprotein mucin 1 (MUC1) promotes cellular adhesion and is expressed in a number of epithelial tissues and carcinomas. MUC1 expressed in malignant cells has been shown to differ structurally from MUC1 expressed in normal tissues. BLP-25 is a liposomal vaccine preparation that targets the exposed peptide core of MUC1 expressed in malignant tissues [36,37].

The MAGE-A3 vaccine is under evaluation in the adjuvant settings. MAGE-A3 is a protein produced almost exclusively by malignant cells that occurs in 35% of NSCLC cases. A phase II randomized, placebo-controlled trial, in patients with completely resected stages IB and II NSCLC reported a trend favoring improved overall and disease-free survival [38].

Study with compounds targeting CTLA-4, PD-1, and PDL-1 have led to the introduction of Nivolumab and Pembrolizumab in the NSCLC therapy.

The PD-1 receptor is a coinhibitory receptor present on T cells and binding of ligands PD-L1 or PD-L2 (produced by tumor or stromal cells) to PD-1 results in inhibition of antitumor immune responses [39].

Ipilimumab was also tested in clinical trials but its real clinical benefit in NSCLC is unclear. The combination of phased ipilimumab and chemotherapy is also being evaluated in the neoadjuvant settings for patients with early-stage NSCLC (NCT01820754) [40]. The PACIFIC study presented at the 2017 Congress of the European Society for Clinical Oncology (ESMO) may change clinical practice. It is a randomized, double-blind, international, phase 3 study comparing durvalumab as a consolidation therapy with placebo in patients with stage III, locally advanced, unresectable NSCLC that had not progressed after platinum-based chemoradiotherapy. Median progression-free survival, as assessed by means of blinded independent central review, was 16.8 months (95% confidence interval [CI], 13.0 to 18.1) with durvalumab versus 5.6 months (95% CI, 4.6 to 7.8) with placebo (stratified hazard ratio for disease progression or death, 0.52; 95% CI, 0.42 to 0.65; two-sided $P < 0.001$). The analysis of across all prespecified subgroups reveal a progression-free survival benefit with durvalumab. Overall survival was not calculated for the moment. The objective response rate with durvalumab had a statistical significant difference than with placebo (28.4% vs. 16.0%; $P < 0.001$). Tolerance and treatment safety were acceptable in the 2 arms of the study; adverse events of any grade occurred in 96.8% of the patients who received durvalumab and 94.9% of the patients who received placebo. Grade 3 or 4 adverse events occurred in 29.9% in durvalumab arm and 26.1% in placebo arm. This study will have an impact in changing the therapeutic protocol where durvalumab could become the standard in adjuvant therapy in patients with stage III disease after usual treatment represented by chemotherapy [41].

Conclusion

Based on several randomized trials and meta-analyses, adjuvant chemotherapy is the accepted standard of care for patients with stage II, IIIA or large (≥ 4 cm) IB non-small cell lung cancer. The survival improvement with adjuvant chemotherapy is approximately 5% at 5 years, though certain trials have suggested that it can be 8% to 10%. The combination of cisplatin and vinorelbine is the most well-studied regimen, but current consensus is to use four cycles of any of the platinum-based chemotherapy regimens. There are trials evaluating the utility of these targeted agents as adjuvant therapy and some positive results are available based on the benefit observed with targeted agents in patients with advanced-stage disease and driver genetic alterations in their tumors. Recent ADAURA study with osimertinib versus placebo will change the paradigm of NSCLC adjuvant therapy. Similarly, clinical benefit observed with checkpoint inhibitors has lead to prompted assessment of these drugs in patients with resected NSCLC. It is very likely that the choice of systemic therapy will extend beyond platinum-based chemotherapy in the future.

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