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Short Review

Developments in the Treatment of Non-small Cell Lung Cancer

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Abstract. *Lung cancer remains the leading cause of cancer-related deaths among men and women in the developed world. Although there have been major improvements over the recent decades in surgical techniques and the role of chemotherapy-radiotherapy in the treatment of non-small cell lung cancer (NSCLC), the long-term outlook for these patients has not changed significantly. The median survival for patients with advanced-stage NSCLC treated with platinum-based chemotherapy is a disappointing 8-10 months. In current clinical practice, chemotherapy is used as a combined modality with radiotherapy as an adjuvant or neoadjuvant therapy. Moreover, combination chemotherapy is regarded as the standard care in the treatment of unresectable locally advanced (stage IIIb), metastatic (stage IV), or recurrent disease. The recent developments in the treatment of NSCLC have been focused on the emerging role of adjuvant therapy in the early stages of NSCLC. The clinical activity of pemetrexed, a multi-targeted antifolate anticancer agent, as a second-line chemotherapy agent and the impact of new biological agents, such as bevacizumab and erlotinib, have been investigated in phase III trials in the first- and second-line setting. Even though these options have been available in the last few years, there is a clear need for improvement in the current standard of care. No definite survival benefit has yet been demonstrated. An abundant amount of research is still required in the field of lung cancer therapy with well-designed clinical trials and appropriate patient selection.*

There are multiple levels of approaching lung cancer management in our medical scientific society such as thoracic surgery for early stages of NSCLC, chemoradiation therapy of locally advanced NSCLC or systemic chemotherapy of metastatic NSCLC. It was estimated in the United States that in 2007 there will be approximately 174000 new diagnoses of lung cancer from which 162000 deaths would result (1).

Regardless of the cancerous cell origin, prognosis is uniformly dismal in any advanced disease, even though 80% of lung cancer cases are of the non-small cell type and the primary therapy is systemic chemotherapy. Moreover, the 5-year survival for lung cancer has remained at <15% for the past 20 years (2). Given the above data, it is realized that a number of therapeutic strategies have to be investigated to improve the overall survival, symptoms and quality of life of lung cancer patients.

The recent developments in the treatment of NSCLC have been focused on the emerging role of adjuvant therapy in the early stages of NSCLC. The clinical activity of pemetrexed, a multi-targeted antifolate anticancer agent, as a second-line chemotherapy agent and the impact of new biological agents, such as bevacizumab and erlotinib have been investigated in phase III trials in the first- and second-line setting.

Adjuvant Chemotherapy

In 1995, the Non-Small Cell Lung Cancer Collaborative Group published a meta-analysis that evaluated the role of cisplatin-containing regimens in all stages of this disease. It included 14 randomized trials of surgery with or without adjuvant chemotherapy in NSCLC; eight of these studies employed cisplatin-based regimens. In this analysis of 1394 patients, there was a 5% improvement in overall survival at 5 years which did not reach statistical significance. In addition, there was also a 13% reduction in the risk of death, which was borderline to statistical significance, using cisplatin-based adjuvant chemotherapy compared with those on observation alone (3). This led to the planning and execution of multiple national and international trials that were adequately powered to look for this 5% improvement in overall survival at 5 years.

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Following this meta-analysis, several randomized clinical trials were performed in the past decade in order to address the role of adjuvant chemotherapy. Three of these studies, the ECOG (Eastern Cooperative Oncology Group) trial (4), ALPI (Adjuvant Lung Project Italy) trial (5), and BLT (Big Lung Trial) trial (6) demonstrated no survival benefit with the addition of adjuvant therapy.

At the beginning of 2004, a large adjuvant phase III study which tested uracil-tegafur (UFT) for 2 years *versus* control in resected stage I adenocarcinoma of the lung was published and the results at 5 years showed a modest, but significant overall survival benefit for UFT-treated patients that was essentially confined to T2 patients (7).

Although a meta-analysis of six of these UFT studies became recently available (8), supporting a role for UFT as an adjuvant treatment, the absence of any advantage in disease-free survival for all UFT-treated arms clearly contrasted with the recently reported positive results of, cisplatin-based adjuvant studies (IALT, NCIC-BR10, CALGB 8633, and ANITA). These studies showed that there was improvement in overall survival which was invariably associated with similar or greater magnitude of the disease free survival.

In the IALT (International Adjuvant Lung Trial) trial (9), 1867 patients were randomized within 60 days of surgery to either cisplatin-based chemotherapy after complete surgical resection or to no chemotherapy at all. In this trial, there was a statistically significant 4.1% absolute survival benefit at 5 years, validating the findings of the 1995 meta-analysis. There were no significant correlations with other factors, including age, sex, stage of disease, type of surgery, histological subtype, or performance status, suggesting that the beneficial effects of chemotherapy could be seen in all these categories.

The National Cancer Institute of Canada (NCIC) JBR 10 study was another positive adjuvant trial, where 482 patients with completely resected stage IB and stage II NSCLC were randomized within 40 days either to observation or to four cycles of cisplatin/vinorelbine (10). The investigators reported a significant 15% survival advantage at 5 years mainly for stage II patients receiving adjuvant therapy.

Another randomized trial was the Cancer and Leukemia Group B (CALGB) study in which 344 resected patients with stage IB disease were randomized to either observation or to 4 cycles of adjuvant carboplatin and paclitaxel (11). The survival advantage for the chemotherapy arm was similar to that seen in the NCIC JBR 10 trial. The results of these two trials were important as they were the first trials of third-generation platinum-based combination therapies to be reported, and both demonstrated a significant survival benefit.

The Adjuvant Navelbine International Trialist Association (ANITA) trial recently presented at the 2005 American Society of Clinical Oncology Meeting, was a randomized study of 840 patients with resected stage IB-IIIA disease to the same cisplatin/vinorelbine regimen used in the NCIC JBR 10 trial. It showed an 8% absolute survival benefit at 5 years for patients receiving adjuvant therapy (12). Subset analysis of the ANITA trial demonstrated that significant improvement in survival was restricted to stage II and IIIA patients and no benefit was observed in stage IB disease. The investigators recommend cisplatin-vinorelbine as standard of care after total resection for stages IIA, IIB, and IIIA.

Taken together, from all the above trials it is recognized that there is indeed a clear role for adjuvant platinum-based chemotherapy for early stage NSCLC after curative resection in those patients with good performance status. In the future, molecularly targeted therapy like that with EGFR-inhibitors and VEGF-inhibitors may play a role for adjuvant treatment of early stage NSCLC. This is based on a particular molecular signature of the tumor that predicts benefit from a specific targeted therapy. The NCIC-CTG BR 19 study is currently assessing the value of adjuvant gefinitib in patients with completely resected stage IB, II, or IIIA NSCLC. Patients are randomized to receive 250 mg gefitinib daily for two years, or a placebo after undergoing resection. In a similar phase III trial sponsored by Roche/Genetech, patients with completely resected stage IB to IIIA NSCLC will be randomized to receive 150 mg erlotinib daily for two years, or to observation alone.

Chemotherapy for Advanced-stage or Metastatic NSCLC

Chemotherapy has become a key treatment for advanced-stage or metastatic NSCLC in the last decade and treatment with dual-agent platinum-based chemotherapy has been the standard of care (13-20). The use of cisplatin over carboplatin results in a modest improvement in survival that is likely offset by its increased toxicity. Non-platinum based regimens with third generation agents are acceptable alternatives to platinum- based therapy (21, 22). Despite the undoubted gains from chemotherapy for stage IIIB or IV NSCLC patients, a proportion of approximately 50% of those who have received first-line platinum-based regimens will relapse during treatment or soon after completion. These patients might be young, with good performance status, and their disease is expressed with only minor symptoms. There is a clear need for these patients to receive second-line chemotherapy in order to achieve a small prolongation in survival (23-26).

Until recently, the role of second-line chemotherapy was undefined. However, after two large phase III randomized trials where single agent docetaxel was compared with best supportive care, or ifosfamide, or vinorelbine, in patients

having failed cisplatin-based first-line chemotherapy, docetaxel has been the leading drug as a second-line therapy (27, 28).

On August 19, 2004, pemetrexed a new generation antifolate anticancer agent that inhibits several folate-depended enzymes required for production of DNA and RNA intermediates received accelerated approval as a monotherapy for the treatment of patients with locally-advanced or metastatic NSCLC who had received prior chemotherapy. Approval was primarily based on a single, controlled, unblended trial (29). Five hundred and seventy-one protocol-eligible patients were randomized to receive either pemetrexed plus vitamin supplementation or docetaxel. In this study, response and clinical benefit rates (CR/PR/SD) were similar in patients receiving either pemetrexed or docetaxel. Patients who had a clinical benefit with first-line chemotherapy were more likely to have clinical benefit with second-line therapy on this trial. Patients with stage III disease (*vs.* stage IV disease), PS 0 or 1 (*vs.* 2), or were >3 months (*vs.* <3 months) since their last chemotherapy, benefited more with second-line chemotherapy on this trial. All efficacy end-points, including overall survival time (median 8.3 *vs.* 7.9 months) and 1-year survival rate (29.7%), were clinically comparable between treatment arms. Although there was clinical equivalent efficacy demonstrated between these two agents, there were several clinically and statistically significant differences in their toxicity profiles. There were higher rates of neutropenia (with and without complications) and more frequent use of G-CSF for patients on the docetaxel arm when compared to the pemetrexed arm. An increase in Serum glutamate pyruvate transaminase (SGPT) was the only toxicity that was higher in the pemetrexed arm. Overall, the rates of improvement or stabilization of baseline symptoms were similar between the two arms. Based on these results, treatment with pemetrexed is considered a standard treatment option for second-line therapy of NSCLC.

Biological Agents

A better understanding of the biology of lung cancer has led to the development of novel therapies directed at tumor-specific targets. Most of these targets are tumor growth factor signal pathways but tumor proliferation, angiogenesis, or apoptosis may also be targeted, particularly by targeting the epidermal growth factor receptor (EGFR) pathway since overexpression of EGFR is found in NSCLC. Erlotinib and gefitinib inhibit the tyrosine kinase activity of EGFR and have been extensively evaluated in NSCLC (30, 31).

The possible role of gefitinib as a second- or third-line treatment for patients with advanced NSCLC, who were refractory or intolerant to their latest chemotherapy regimen, was examined in a phase III clinical trial (ISEL trial) (32) . In this study, 1692 patients were randomized to receive either gefitinib (n=1129) or a placebo (n=563). After a median follow-up of 7 months, the investigators reported no difference in overall survival (5.6 months for gefitinib and 5.1 months for placebo). Longer survival on the gefitinib arm was observed in patients with Asian ethnicity or nonsmokers, but not adenocarcinoma histology. The discovery that patients responsive to gefitinib have mutations in the exons of EGFR gene coding has opened new possibilities in the area of targeted therapy.

Of vital importance is the result of a phase III randomized placebo control trial (BR 21 study) in which erlotinib was administered to patients with advanced NSCLC (stage III/B and IV) after failing one or two lines of chemotherapy (33). In this study, 731 patients were randomly assigned in a 2:1 ratio for erlotinib, to receive either oral erlotinib or placebo. The overall response rate to erlotinib was 8.9% and less than 1% in the placebo group ($p<0.001$) with a median duration of response 7.9 months and 3.7 months, respectively. Overall survival was 6.7 months for the erlotinib group *versus* 4.7 months in the placebo group ($p<0.001$). The most common adverse effects in the erlotinib group were skin toxicity, diarrhea and infections. Twenty-six patients (5%) discontinued erlotinib due to drug-related toxic effects compared to 4 patients (2%) who received placebo. In a multivariate analysis, objective response was significantly associated with never smokers, adenocarcinoma histology, and expression of EGFR by IHC. Notably, the presence of EGFR gene mutations was not predictive of a survival benefit from erlotinib in this study (34). This is the first study demonstrating that EGFR tyrosine kinase inhibitors may prolong survival after chemotherapy in NSCLC, and has also led to the approval of erlotinib by the Food and Drug Administration (FDA) for the treatment of NSCLC after failure of first-line treatment.

More recently, the Eastern Cooperative Oncology Group reported a phase III trial (ECOG 4599) comparing the same chemotherapeutic combination (paclitaxel-carboplatin) with or without bevacizumab at a dose of 15 mg/kg every 3 weeks. The study was organized in 878 chemonaïve patients with advanced NSCLC (35). Analyses of this study showed an improvement in response (10% *vs.* 27%), progression-free survival (4.5 *vs.* 6.2 months) and median survival time (10.3 *vs.* 12.3 months) with the bevacizumab group. Given information from a phase II trial (36), patients with squamous cell disease, central nervous system metastases and a history of hemoptysis, coagulopathy, or thrombosis were excluded. Unfortunately, the bevacizumab arm was correlated with higher rates of toxicity, including a larger number of treatment-related deaths (9 *vs.* 2). Although fatal hemoptysis was seen in the bevacizumab arm (5 of the 9 deaths), the difference was not statistically significant

between the two arms. In addition, even though an observation of prolonged response rate and time to progression was seen with the women in the bevacizumab arm, an increase in overall survival was not achieved.

These results are quite promising for the role of bevacizumab in addition to the conventional double chemotherapy in patients with advanced NSCLC.

Conclusion

Although advanced NSCLC cannot be approached with curative intent, we need to respect the dogma "The absence of proof is not a proof of absence", and evaluate well-designed clinical trials with appropriate patient selection, as well as continued efforts in translational research and pharmacogenomics, in order to achieve progress in this disease.

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