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REVIEW ARTICLE

Chemotherapy In Advanced Non-Small Cell Lung Cancer: A Review

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ABSTRACT

Treatment of advanced non small cell lung cancer (NSCLC) has been a challenge for oncologists in the past two decades. Meta-analysis conducted decade determined that cisplatin based chemotherapy prolonged survival in advanced NSCLC. Since then various combinations of cytotoxic agents like gemcitabine, docetaxel, paclitaxel and vinorelbine with either cisplatin or carboplatin have made undeniable gains in survival rates among the patients with advanced NSCLC and this has been confirmed by various randomized studies between 1991 and 2001. This article gives a critical appraisal of published data related to chemotherapeutic approaches for advanced NSCLC including a recent meta-analysis which aims to quantify the treatment effect of gemcitabine plus platinum agents in advanced NSCLC using randomized clinical trials. The evidence suggests an improvement in progression free survival for gemcitabine-platinum compared to other agents. Some encouraging data about various targeted therapies (Eroltinib and Gefitinib) in advanced NSCLC has also been discussed.

Key Words : *NSCLC, Chemotherapy, targeted therapy*

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Introduction

Lung cancer is one of the most common cancers in the world, in terms of incidence and mortality with over one million new cases annually[1]. Non Small Cell Lung Cancer (NSCLC) accounts for atleast 80% of all lung cancer cases, presenting as locally advanced disease in approximately 25-30% of cases and as metastatic disease in approximately in 40-50% of cases[2]The use of chemotherapy in patients with NSCLC has been under investigation for several decades. It has evolved from administration in the palliative care setting to the integration into combined modality

curative therapy settings in patients with locally advanced disease. Prior to 1993, attempts to identify new chemotherapeutic agents and combinations with activity against NSCLC met with little success. Recently, however, several new compounds have offered hope for some improvement in response and survival while being relatively well tolerated in patients with this disease. A wide- reaching meta-analysis conducted during last decade suggested that cisplatin-based chemotherapy prolonged survival in advanced NSCLC, and an addition of third generation cytotoxic agent like gemcitabine, taxanes and vinorelbine with either cisplatin or carboplatin have made definite gains in the survival rates for the patients with advanced NSCLC.

Review of Meta-Analysis

There are incremental advances in the treatment of NSCLC during the last two decades. Platinum based combination chemotherapies emerged as the standard treatment for advanced NSCLC[3],[4].. Randomized studies from 1980's reported survival gains with cisplatin based chemotherapy over best supportive care, which was confirmed by a large meta-analysis of cisplatin based chemotherapy that estimated significant increases in median survival of 1.5 months and 1 year survival of 10% [5]. A 1995 meta-analysis of chemotherapy in patients with advanced non-small cell lung carcinoma indicated clinical benefit from cisplatin based chemotherapy. Subsequent studies have aimed

either to increase the efficacy or decrease the toxicity of chemotherapy. [Table/Fig 1][6]

Table/Fig 1 Meta-analysis of randomized trials of adjuvant chemotherapy[6]

Study (%)	Number of patients	Stage	Chemotherapy	5-Year Survival
IALT	1867	I–IIIA	Cisplatin & etoposide/ vinorelbine/vindesine/ vinblastine	4.1
BLT	381	I–III	Cisplatin-based	No benefit
ALPI	1209	I–IIIA	MVP	3
CALGB	344	IB	Carboplatin–paclitaxel	3
BR10	482	IB–II	Vinorelbine–cisplatin	15
ANITA	840	I–IIIA	Vinorelbine–cisplatin	8

Reviews from various studies and meta analyses of different aspects of chemotherapy which have taken place over the last decade, suggest that the use of third generation chemotherapy agents has resulted in a further increase in patient survival. Gemcitabine was shown to be associated with an increase in progression free survival (PFS) when compared to other third generation agents as well as a strong tendency to increased overall survival. An increase in survival was also shown with doublet chemotherapy regimes as compared to the use of single agents only. The use of triplet agent chemotherapy results in no further increased survival, but increased toxicity. Cisplatin is associated with increased survival over carboplatin based chemotherapy regimens when third generation agents are used, but increased nausea and vomiting. Non-platinum third generation combinations give equivalent survival to platinum-based regimens. Thereby a conclusion was drawn that, the first line chemotherapy given to patients with advanced NSCLC should be two-drug combination regimen. Non-platinum containing regimens may be used as an alternative to platinum based regimens in the first line[7].

A recently published data on meta-analysis of survival outcomes in advanced NSCLC (4556 patients from 13 randomized trials) aims to quantify the treatment effects of gemcitabine plus a platinum agent, cisplatin or carboplatin, in the treatment of advanced NSCLC using randomized clinical trials[8]. The primary comparator was any regimen containing a platinum agent alone or in combination. The main out come of interest was overall survival. The result of this meta-analysis suggests a significant reduction in overall mortality in favor of gemcitabine-platinum regimen, hazard ratio (HR) 0.90 (95% CI: 0.84-0.96) with an absolute benefit of 3.9% at 1year. Median survival was 9 months for gemcitabine-platinum regimen and 8.2 months for the comparator regimen. There was a significant reduction in the risk of disease progression in favor of gemcitabine-platinum regimen, HR 0.88 (CI: 0.82-0.93). An absolute benefit of 4.2% at one year was estimated. Median PFS was 5.1 months for gemcitabine-platinum regimen compared with 4.4 months for the comparator regimen. Subgroup analysis indicated a statistically significant PFS benefit for patients assigned to gemcitabine-platinum treatment compared to first and second generation platinum regimen, HR 0.85 (CI:0.77-0.94) and third generation agent plus platinum regimen, HR 0.89 (0.82-0.96).

Review of Results from Phase II& Phase III Trials

Modern platinum-based combination therapies containing gemcitabine, vinorelbine or taxanes produce response rates of 30-40%, median survival times of 8-10 months and 1-year survival rates of approximately 35% in patients with advanced non-small-cell lung cancer (NSCLC). Of the new drugs available, gemcitabine has been the most extensively researched in clinical trials and exhibits a consistent database. A total of 37 randomized phase III trials involving more than 15,000 patients have been published to evaluate gemcitabine as first-line therapy for treating locally advanced and/or metastatic NSCLC[9]. One trial studied gemcitabine exclusively as a single agent and another four trials investigated the drug in monotherapy and combination therapy. Of the 36 combination treatment studies, 21 included gemcitabine plus cisplatin treatment arms, 6 investigated gemcitabine plus carboplatin, and another 12 evaluated platinum-free gemcitabine combinations with other third generation cytostatic agents (multiple nominations possible). In single-agent treatment, gemcitabine was similarly effective to older platinum-based combinations such as vindesine-cisplatin but was less toxic. Thrombocytopenia was the main dose-limiting toxicity but was rarely clinically relevant. A 3-week cycle with gemcitabine on days 1 and 8 was confirmed as being the most convenient of the gemcitabine-based combinations studied. No other modern platinum-based doublet with vinorelbine or taxanes was superior to gemcitabine plus cisplatin in terms of survival or

time to progression in any of the eight phase III studies performed. These results are consistent with previous phase II data and with a recent meta-analysis of 11 phase III and 2 randomized phase II studies involving more than 4,500 patients (1,861 in gemcitabine-based treatment arms). This meta-analysis also demonstrated a statistically significant benefit regarding overall survival and PFS for gemcitabine-platinum- based regimens compared with other platinum combinations. In summary, currently available data indicate that gemcitabine-platinum two-agent combinations given in 3-week cycles may at present have the best risk benefit ratio in the treatment of advanced NSCLC. In contrast, platinum based 3-agent schedules do not offer any survival benefit. In elderly patients with poor performance status single agent treatment should be considered.

The results of a phase II trial using Gemcitabine as a single agent are recently published[10]. This trial was designed to determine the 1-year survival rate, efficacy, PFS, and toxicity with Gemcitabine in patients with stage IIIB (with pleural effusion) or stage IV non-small-cell lung cancer (NSCLC) with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2. Gemcitabine 1250mg/m2 was administered intravenously on days 1 and 8 of each 21-day cycle. Treatment consisted of 6 cycles; patients who responded with complete response or partial response received ≥ 2 additional cycles. Forty-two patients were enrolled at 31 community-based centers between March and November 2002. Most patients had stage IV disease (74%). The median age was 73 years (range, 58-84 years), and 19% had received prior palliative radiation therapy. Patients received a median of 3 cycles (range, 1-8 cycles). The median survival was 4.8 months (range, < 1 to 19.2 months), and the estimated 1-year survival was 20%. Median PFS was 2.5 months (range, < 1 to 19.2 months), and PFS at 1 year was 11.1%. Thirty-one patients died of disease progression, and one each died of myocardial infarction, brain herniation, pneumonia, and respiratory failure. Seven patients were not evaluated for response; four refused or received no treatment, treatment in two failed (myocardial infarction and pneumonia), and one was lost to follow-up. Among 35 evaluated patients, there were 5 partial responses (14%), 10 with stable disease (29%), and 20 with disease progression (57%). Drug-related grade ≥ 3 toxicities included neutropenia (18%), anemia (8%), and dyspnea (2.6%). These results suggest that patients with NSCLC with an ECOG PS of 2 may benefit from single-agent chemotherapy Gemcitabine. General toxicity, including myelo toxicity, was relatively low. Further studies comparing single-agent chemotherapy with combination chemotherapy for patients with a PS of 2 are warranted.

The large phase III studies performed with doublets containing new drugs and platinum are not free of criticism. The biggest criticism is the failure to indicate a standard regimen in the research involving more than 3000 patients. With the aim to strengthen the phase III studies results, a meta-analysis tested the survival outcomes of published randomized trials, analyzing the effects of the combination of Gemcitabine and platinum compounds versus any platinum-based regimens. Gemcitabine-platinum combinations appear to offer a statistically significant superior efficacy in terms of overall survival and progression free survival as compared to other platinum-based regimens. Considering the palliative role of chemotherapy in advanced NSCLC and in order to reduce toxicity, no cisplatin containing regimens were investigated. The results support the suggestion from the last ASCO guidelines: first-line chemotherapy of advanced NSCLC should be a two-drug combination regimen and non platinum-based chemotherapy may be used as alternative to platinum-based regimens[10].

Neoadjuvant Chemotherapy:

Neoadjuvant treatment followed by surgery is currently being investigated for locally advanced non-small cell lung cancer (NSCLC). This study reports efficacy, toxicity and feasibility of neoadjuvant chemotherapy with concurrent radiotherapy (CCRT) in stage IIIA, N2 positive NSCLC. .From March 2001 to February 2004, 52 patients with histologically confirmed stage IIIA, N2 positive NSCLC was registered. Patients received preoperative CCRT that consisted of weekly paclitaxel plus platinum chemotherapy and concurrent radiotherapy followed by surgery. Overall response rate was 76.9% (95% CI, 64-88%). The major grade III-IV toxicities were radiation esophagitis (15.4%) and neutropenia (11.5%), and treatment-related mortality rate was 1.9%. Forty-two of 52 patients (80.8%) subsequently underwent surgical resection and 35 of 52 patients (67.3%) underwent complete resection. Among them, pathological complete response was obtained in 4.8%. Pathological

down staging rate to N0-1 and stage 0-II at surgery were 69.0% and 66.7%, respectively. The peri-operative major morbidity rate was 23.8% and peri-operative mortality was 2.4%. At a median follow-up of 33.9 months (range: 16.4-49.9), the median progression-free survival and overall survival were 16.5 months (95% CI, 6.2-26.8) and 25.6 months (95% CI, 14.6-36.6), respectively. Multivariate analyses identified that patients achieved mediastinal nodal clearance (downstage to pathological N0 or N1) after CCRT ($p=0.02$) and age at diagnosis<60 years ($p=0.01$) showed significantly improved survival, thus concluding that Neoadjuvant CCRT showed a high overall response rate with tolerable toxicity profile. Down staging after CCRT may increase the rate of complete tumor resection and result in survival benefit in stage IIIA, N2 positive NSCLC patients[11].

Role of Taxanes

This evidence-based practice guideline on the use of paclitaxel (Taxol) or docetaxel (Taxotere) as first-line treatment for patients with advanced non-small cell lung cancer, who are candidates for palliative first-line chemotherapy is based on a systematic search and review of literature published in full or in abstract form between 1985 and April 2005. Forty-five randomized trials, including 11 abstracts, were reviewed and clinicians in the province of Ontario, Canada, provided feedback on a draft version of the guideline. Two phase III trials detected a statistically significant survival advantage for a taxane (paclitaxel or docetaxel) with best supportive care versus best supportive care alone. Among the nine fully published phase III trials comparing platinum-based chemotherapies, taxane-platinum combinations achieved higher response rates compared with older chemotherapy combinations, although significantly longer survival was observed only for docetaxel-cisplatin compared with vindesine-cisplatin. Response rates and survival were generally not significantly different for taxane-platinum combinations compared with other current chemotherapy combinations, although the toxicity profile of the regimens varied. However, in one large trial, improved tumor response and modest survival and quality of life benefits were associated with docetaxel-cisplatin compared with vinorelbine-cisplatin. No statistically significant survival differences were detected in the three fully published phase III trials comparing a taxane-gemcitabine combination with a taxane-platinum regimen. On the basis of above studies , the recommendations are;- (i) paclitaxel or docetaxel combined with cisplatin is recommended as one of a number of chemotherapy options for the first-line treatment of advanced non-small cell lung cancer in patients with a good performance status; (ii) carboplatin may be combined with a taxane if a patient is unable or unwilling to take cisplatin; (iii) a taxane-gemcitabine combination may be considered for patients with a contraindication to cisplatin and carboplatin; (iv) no firm recommendation can be made on the optimal dose and schedule of taxane-based chemotherapy; however, commonly used regimens include cisplatin 75 mg/m2 combined with either docetaxel 75 mg/m2 or paclitaxel 135 mg/m2 (24-h infusion) and carboplatin AUC 6 combined with paclitaxel 225 mg/m2 (3-h infusion); (v) a single-agent taxane may be used if combination chemotherapy is considered inappropriate[12].

Targeted Therapies

Bevacizumab is a recombinant, humanized monoclonal antibody against vascular endothelial growth factor. Erlotinib HCl is a reversible, highly selective epidermal growth factor receptor tyrosine kinase inhibitor. Additionally, both agents have shown benefit in patients with previously treated non-small cell lung cancer (NSCLC). Preclinical data in xeno-graft models produced greater growth inhibition with the combination than with either agent alone. A phase I/II study in two centers examined combined erlotinib and bevacizumab treatment in patients with nonsquamous stage IIIB/IV NSCLC with one or more prior chemotherapy. In phase I, 150 mg/d erlotinib orally plus 15 mg/kg bevacizumab i.v. every 21 days was established as the phase II dose. A total of 40 patients were enrolled and treated in this study (34 patients at phase II dose): 21 were female, 30 had adenocarcinoma histology, 9 were non smokers, and 22 had two or more prior regimens. The most common adverse events were mild to moderate rash, diarrhea, and proteinuria. Preliminary data showed no pharmacokinetic interaction between erlotinib and bevacizumab. Eight patients (20.0%) had partial responses and 26 (65.0%) had stable disease as their best response. The median overall survival for the 34 patients treated at the phase II dose was 12.6 months, with progression-free survival of 6.2 months. Encouraging anti tumour activity and safety of erlotinib plus bevacizumab support further development of this combination for patients with advanced NSCLC. A randomized

phase II trial has been completed, and a phase III trial is ongoing[13].

The epidermal growth factor receptor (EGFR) inhibitors erlotinib, gefitinib, and cetuximab have undergone extensive clinical testing and have established clinical activity in non-small cell lung cancer and other types of solid tumors. A number of newer inhibitors are currently in clinical development with different spectra of activity or mechanisms of receptor inhibition. These include monoclonal antibodies, such as panitumumab and matuzumab; dual inhibitors of EGFR and vascular endothelial growth factor receptor, such as ZD6474 and AEE788; inhibitors of multiple EGFR family members, such as lapatinib; and irreversible inhibitors, such as canertinib and HKI272. Preclinical studies suggest that several of these agents may have activity in tumors refractory to erlotinib or gefitinib. Among these agents, ZD6474 has undergone the most extensive clinical testing. The antitumour activity of ZD6474 in these two randomized phase II clinical trials in patients with non-small cell lung cancer was felt to be sufficiently promising to warrant phase III clinical testing. Several of the other EGFR inhibitors are also undergoing advanced clinical testing, either alone or in combination with other agents. EGFR has now been validated as a clinically relevant target, and several different types of agents inhibiting this receptor are currently in development. Future research will be needed to elucidate the role of these agents in patients with EGFR inhibitor-naive and EGFR inhibitor-refractory disease, to define the molecular characteristics that predict response, and to determine whether these drugs should be used in combination with other targeted agents or chemotherapy[14].

Discussion

Gemcitabine is one of the most active drugs approved for advanced NSCLC in recent years. It is a novel nucleoside analogue exercising a wide spectrum of anti tumoural activity, and in combination with cisplatin has activity in NSCLC. Several phase II studies of gemcitabine plus cisplatin reported median survival times of[15],[16],[17],[18],[19] months and response rates of 40-50% while phase III studies showed superiority of gemcitabine plus cisplatinum in advanced NSCLC in terms of both survival and QOL benefits when compared with platinum alone or in combination with older chemotherapy agent[17],[18] Gemcitabine plus cisplatin is widely used in clinical practice globally, and in several European countries has become a common doublet for treatment of advanced NSCLC. Replacement of cisplatin with carboplatin is attractive because it avoids cisplatin side effects and administration requirements. The combination of gemcitabine and carboplatin has been shown to be feasible and active in various recent clinical trials[19],[20],[21].

The recently published report on meta-analysis of survival outcomes of advanced NSCLC evaluated a large data of 4556 patients from 13 randomized clinical trials. Since 1995 ten primary meta-analyses have been published on NSCLC[9],[22],[23] and out of these ten, two used individual patient data while the remaining used summary data from published sources. The meta-analysis ranges from several trials and 700 patients to 25 trials and 5156 patients.

Treatment with gemcitabine-platinum regimens produced a statistically significant reduced risk of mortality with an absolute benefit on OS of 3.9% at one year and 2.6% at two years. This benefit translates to 1039 gemcitabine-platinum treated patients alive at one year compared to 1000 non gemcitabine-platinum treated patients. The estimated difference in median survival of 3 weeks for gemcitabine-platinum regimen represents a slight, but meaningful improvement in median survival in NSCLC (9.0 months versus 8.2 months). The treatment benefit obtained from using meta-analysis is enough evidence for use by consolidating data of individual trials.

Based on the above results, it is possible to conclude that NSCLC patients today are receiving treatment that is superior in terms of efficacy to treatment 10 years ago. The meta-analysis also suggests an improvement in progression free survival for gemcitabine-platinum compared to other third generation agent platinum combination, as well as a clear trend towards improved survival, although the latter just missed statistical significance, making the gemcitabine-cisplatinum doublet a reference regimen not surpassed by any of the other current doublets.

Genomic and proteomic studies have started to shed new light on the biology of NSCLC[24], [25]. Gene mutations have been discovered that predict clinical benefits from treatment with the EGFR tyrosine kinase inhibitor gefitinib[26]. The day is not far when the patient will receive treatment that gives them the best chance of benefit while sparing them from toxicity associated with treatment that they likely would not benefit from. Until then, the oncologist should

select the chemotherapy regimen based on probability of survival benefit balanced by the toxicity profile.

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