

Chemotherapy Improves Quality of Life and Prolongs Survival in Patients of Lung Cancer

Sameer Singhal¹, Prachi Singhal², Abinav Dagar³, Atulya Atreja⁴, Ankit Sharma³, Himanshu Sharma³

ABSTRACT

Lung cancer is the most frequently diagnosed cancer and the foremost cause of cancer-related deaths. Particularly, lung cancer has an estimated incidence of 1.6 million new cases every year. Despite the various advances made in combined therapies and surgical techniques, it remains a disease with a dismal prognosis. Although one year survival has improved over the past few decades due to the availability of advanced diagnostic, genetic technologies, surgical techniques and formulation of newer biologic treatments. Chemotherapy markedly prolongs survival as compared to supportive care in patients of lung cancer. In this article we reviewed different randomized controlled trials on chemotherapy in order to assess the impact of anti-cancer treatment on quality of life in lung cancer patients and to be able to choose an appropriate regimen of therapy for lung cancer patients.

Keywords: Lung Cancer, Chemotherapy, Survival, Supportive Care, Regimen

INTRODUCTION

Lung cancer is the most frequently diagnosed cancer and the foremost cause of cancer-related deaths. Particularly, lung cancer has an estimated incidence of 1.6 million new cases every year. Lung cancer is classified into two main subtypes based on their histological characteristics: Small cell lung cancer (SCLC) and Non small cell lung cancer (NSCLC). NSCLC and SCLC constitute 85% and 15% of total lung cancer cases respectively. Only 16.6% of lung cancer patients survive 5 years or more, with only 3.9% surviving in the metastatic setting.¹ Despite the various advances made in combined therapies and surgical techniques, it remains a disease with a dismal prognosis. Although one year survival has improved over the past few decades due to the availability of advanced diagnostic, genetic technologies, surgical techniques and formulation of newer biologic treatments, the overall five year survival rate for lung cancer remains almost unchanged at around 12% to 16% over the past 30 years.² The geographic region and ethnicity plays an important role in the incidence and pattern of lung cancer and also mostly reflect the pattern and prevalence of smoking. Tobacco smoking is among the oldest and the most well-established risk factor for lung cancer. Its constituents advance lung carcinogenesis through the addition of mutations in key genes in the growth regulatory pathways, causing unrestrained cellular production and tumorigenesis. Exposure to tobacco has found to be seen in about eighty five percent to ninety percent of lung cancer patients with lung cancer.³ Globally, Lung cancer attributes for about thirteen per cent

of all new cancer cases and about nineteen per cent of deaths related to cancer. In India, lung cancer comprises about 6.9 per cent of all new cancer cases and around 9.3 per cent of all deaths related to cancer in both sexes.

In terms of occurrence, Cancer of the bronchus and lung ranked second in cancer in males and females. Around 1.8 million new lung cancer cases were estimated to occur in 2012 with approximately 110,110 newer cases in females (14% of all newly diagnosed cancers) and 118,080 in males (14% of all newly diagnosed cancers).³

The projected increase in total incidence of cancer over the next 15 years is expected to be proportionally higher in low and middle-income countries (LMICs). Due to the rising tobacco use in Low and Middle Income countries, the existing lung cancer epidemic in these areas has not yet reached its peak, and rates would continue to ascend in the future.^{4,5} Environmental factors including air pollution, contamination of drinking water with arsenic and workplace exposure in industries such as mining are also contributing to this transition in the epidemiology of lung cancer.⁵

CHEMOTHERAPY REGIMENS

Small Cell Lung Cancer

Untreated, patients with SCLC rarely survive more than a few months. Chemotherapy markedly prolongs survival compared to best supportive care.² In LS disease, chemotherapy combined with thoracic radiation achieves a response in 80% to 90% of patients, and a complete response in the range of 40% to 60%. In LS disease, median survival in treated patients is 15 to 20 months, with 5-year survival rates of 10% to 13%. In ES disease, the response rate is 60% to 80%, with a complete response rate around 15% to 35%. The median survival for ES patients treated with chemotherapy remains 7 to 9 months, with few long-term survivors.

Agents active against SCLC

- Platinum compounds:- Cisplatin, Carboplatin
- Podophyllotoxins:- Etoposide, Tenoposide

¹Professor and Head, ³Post Graduate Resident, Department of Respiratory Medicine, MMIMSR, ²Reader, Department of Prosthodontics, MMCD SR, Mullana, ⁴Consultant Pulmonologist, Karnal

Corresponding author: Dr Abinav Dagar, #412, Hostel-9, MMIMSR, Mullana

How to cite this article: Sameer Singhal, Prachi Singhal, Abinav Dagar, Atulya Atreja, Ankit Sharma, Himanshu Sharma.

Chemotherapy improves quality of life and prolongs survival in patients of lung cancer. International Journal of Contemporary Medical Research 2018;5(3):C1-C4.

- (c) Camptothecins:- Irinotecan, Topotecan
- (d) Alkylating agents:- Ifosfamide, Cyclofosfamide
- (e) Anthracyclines:- Doxorubicin, Epirubicin
- (f) Taxanes:- Paclitaxel, Docetaxel
- (g) Vinca alkaloids:- Vincristine, Vinorelbine
- (h) Nitrosoureas:- Lomustine
- (i) Anitmtabolites:- Methotraxate

The earliest treatments for SCLC included alkylating agents, such as nitrogen mustard and subsequently cyclophosphamide, given as monotherapy. As responses to single agents were rare, the focus changed to combinations of drugs, each with independent activity against SCLC. When given in combination, these drugs had synergistic activity, and lowered the likelihood of complete tumor resistance. Until the mid-1980s the combination of cyclophosphamide, doxorubicin (Adriamycin), and vincristine (CAV) was commonly used as first-line therapy. For the past three decades, platinum based regimens have become the most frequently used combinations.⁴

Currently, the two-drug regimen of cisplatin and etoposide (PE) is considered the standard of care for SCLC chemotherapy. Modifications to the PE regimen have included the substitution of carboplatin for cisplatin, replacing etoposide (a topoisomerase II inhibitor) with irinotecan or topotecan (topoisomerase I inhibitors), adding other agents, increasing dose intensity, and prolonging the duration of chemotherapy.

Non-Small Cell Lung Cancer

The standard first-line chemotherapy recommendations currently consist of a platinum doublet.

Regimens usually used:-

- (1) Cisplatin+Paclitaxel
- (2) Cisplatin+Gemcitabine
- (3) Cisplatin+Docetaxel
- (4) Carboplatin+Paclitaxel
- (5) Cisplatin+Etoposide

Pemetrexed, an antifolate, is a relatively new addition to the available agents in the first-line setting. This cytotoxic agent is unique in that efficacy varies by the histology of the NSCLC and it is labelled for use in non-squamous cell NSCLC only.

The monoclonal antibody bevacizumab, which targets the VEGF, is approved for first-line treatment of NSCLC and SCLC when combined with cytotoxic chemotherapy.

DISCUSSION

Chemotherapy markedly prolongs survival as compared to supportive care in patients of lung cancer.

The Eastern Cooperative Oncology Group (ECOG) conducted a study comprising eight hundred and ninety three patients having good performance status with metastatic non-small-cell lung cancer (NSCLC) and treated them with combination chemotherapies between December 1979 and June 1983. The median survival rate was found to be 23.5 weeks with out any significant difference among different regimens. One hundred sixty eight patients (19%) survived > 1 year and 36 (4%) for > 2 years. The platinum- etoposide

regimen had the highest percentage of one year survivors (25%).⁶

The National Cancer Institute of Canada (NCIC) Clinical Trials Group conducted a prospective randomized trial in year 1988 comparing best supportive care (BSC) to two chemotherapy regimens, vindesine and cisplatin (VP), and cyclophosphamide, doxorubicin, and cisplatin (CAP) and concluded that chemotherapy improves survival in patients of NSCLC.⁷

Fukuoka M et al conducted a randomized controlled trial in the year 1991 and concluded that the combination of Cisplatin with Etoposide compared with the combination of Cyclophosphamide, Vincristine and doxorubicin was as effective in patients of SCLC with less toxicity profile.⁸

Roberto Grilli et al conducted a meta-analysis in the year 1993, of various Randomized-controlled trials published in medical literature between 1970 and 1991 and found that chemotherapy is an important modality in the management of advanced Non Small cell Carcinoma Lung, However it had minimal impact on the duration of survival.⁹

In a study conducted by Eastern Cooperative Oncology Group Trial in the year 2000 which compared two combinations of Cisplatin+Etoposide with Cisplatin+Paclitaxel in patients of NSCLC found Mean survival time 7.6 months and 1-year survival rate 31.8% for Cisplatin+Etoposide combination and Mean survival time 9.9 months and 1-year survival rate 38.9% for Cisplatin +Paclitaxel combination.¹⁰

In another study conducted by Eastern Cooperative Oncology Group Trial in the year 2002 which compared Four regimens Cisplatin+paclitaxel, Cisplatin+Gemcitabine, Ciaplatin+Docetaxel and Carboplatin+Paclitaxel in Patients of NSCLC and came to a conclusion that all the four chemotherapy regimens offered similar results in the treating advanced non-small-cell lung cancer.¹¹

Giannicola D'Addario et al conducted a meta-analysis in the year 2005 to compare the activity, efficacy and toxicity of platinum based versus non-platinum-based chemotherapy in patients with advanced non-small-cell lung cancer and concluded that response is significantly higher with platinum-containing regimens.¹²

Andrea Ardizzoni et al conducted a meta-analysis in the year 2007 comparing cisplatin based chemotherapy with carboplatin based chemotherapy in first line treatment of NSCLC and found that cisplatin-based regimen is a little superior to carboplatin based regimen in factors like response rate and prolonging survival without increasing the toxicity. Hence he concluded that cisplatin based chemotherapy should be used in treatment of patients with advanced-stage NSCLC and also among those with earlier-stage disease.¹³

In 2009 Alvarez M P et al conducted a meta-analysis of the various RCT's in which a chemotherapy regimen was compared with a placebo in SCLC patients and concluded that chemotherapy prolongs survival in patients of SCLC.¹⁴

Jennifer S. Temel et al conducted a study in the year 2010 on Early Palliative Care for Patients with Metastatic Non-Small-Cell Lung Cancer and came to a conclusion that if palliative

care was given early it led to considerable improvement in both mood and quality of life as when compared to patients who had received standard care.¹⁵

John Goffin et al conducted a systematic review in the year 2010 on first line chemotherapy for Advanced NSCLC and came to a conclusion that a platinum agent when combined a new agent continues to be the desired regimen. The differences between various regimens are minimal and hence toxicity along with patient preference should be used to get the desired regimen.¹⁶

Jean-Charles Soria et al conducted a phase 3 randomized control trial also known as IMPRESS trial published in the year 2015 comparing Gefitinib plus chemotherapy versus placebo plus chemotherapy in *EGFR*-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib and decided that persistence with gefitinib post radiological disease progression on first-line gefitinib did not extend progression free survival in people who were given platinum-based chemotherapy as subsequent line of treatment. Platinum-based regimens remain the standard treatment modality in this setting.¹⁷

Pujol J-L et al conducted a randomized controlled trial published in the year 2015, to evaluate the efficacy and safety of adding bevacizumab (Bev) following induction chemotherapy (CT) in extensive small-cell lung cancer (SCLC) and concluded that Administering 7.5 mg/kg Bev after induction did not improve outcome in extensive SCLC patients.¹⁸

Bob T Li et al conducted a meta-analysis published in the year 2016, of randomized-controlled trials studying, The addition of anti-angiogenic tyrosine kinase inhibitors to chemotherapy for patients with advanced non-small-cell lung cancers and concluded that, the addition of AATKI to chemotherapy in patients with advanced NSCLC significantly increased PFS(Progression Free Survival) and ORR(Objective Response Rate) but not OS(Overall Survival). It did so at the cost of amplified toxicity and treatment related mortality. Translational and Pre clinical research in predictive biomarkers are essential for the expansion of this group of drugs.¹⁹

CONCLUSION

Lung cancer is considered to be the most common cause of deaths related to cancer both in women and men globally, accounting for about one million deaths yearly. Although globally one year survival has improved over the past few decades due to the availability of advanced diagnostic technologies, surgical techniques and formulation of newer biologic treatments, it continues to be a major challenge in our country as vast majority of our population being economically backward does not have access to these facilities.

Cisplatin based chemotherapy improves survival and quality of life in patients of lung cancer. Cisplatin+Etoposide combination chemotherapy can be used as a palliative therapy for both SCLC and NSCLC especially in a rural centre with resource poor patients.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 11-02-2018; **Accepted:** 14-03-2018; **Published:** 25-03-2018