The Influence of the Evolution of First-Line Chemotherapy on Steadily Improving Survival in Advanced Non–Small-Cell Lung Cancer Clinical Trials

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Abstract: Over the past three decades, survival in advanced non–small-cell lung cancer (NSCLC) clinical trials has doubled with an increase in 1-year survival from 25% to 50 to 55%. This has been mainly attributed to improvements in systemic therapy. Although modern first-line chemotherapy regimens have more favorable toxicity profiles, a statistically significant improvement in overall survival has not been demonstrated in existing meta-analyses of second-generation versus third-generation combinations. Moreover, pivotal trials demonstrating statistically significant survival superiority of third-generation regimens are consistently not reproducible even for nonsquamous populations using pemetrexed–platinum combinations. As enhancement in the efficacy of first-line systemic therapy in patients without identifiable driver mutations is questionable, other factors are discussed that explain the doubling of 1-year survival reported in clinical trials. These factors include second-line or third-line therapy, maintenance chemotherapy, performance status selection, stage migration, sex migration, improved treatment of brain metastases, and better palliative care.

Key Words: Non–small-cell lung cancer, Palliative chemotherapy, Critical review.

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Lung cancer is the leading cause of cancer deaths in both males and females with an estimated 224,000 new cases and 159,000 deaths in the United States in 2014 and 26,100 new cases and 20,500 deaths in Canada in 2014.[1,2] Eighty-five percent of lung cancer cases are non–small-cell lung cancer (NSCLC), and because a large fraction of NSCLC patients are diagnosed with advanced disease and many patients relapse from earlier stage disease, more than 80% of this patient population are potential beneficiaries of palliative systemic therapy.[3]

Palliative first-line chemotherapy has been shown to improve both quality of life and survival in advanced NSCLC patients.[3–5] Practice guidelines exist for systemic therapy administration with the intent that most advanced NSCLC patients receive some form of palliative anticancer drug treatment.[6] However, when population-based data are examined, less than half of the advanced NSCLC patient population receive any systemic therapy in United States[7–10] and Canada.[11]

Over the past 30 years, there has been considerable improvement in overall survival (OS) in advanced NSCLC as reported in large randomized controlled trials (Table 1). The median survival and 1-year survival with early platinum combinations were approximately 7 months and 25%, respectively, whereas with the most recent generation of platinum combinations, the median survival has increased to 12 to 13 months, and the 1-year survival is typically 50% to 55%.[12] This impressive doubling of median survival and 1-year survival is similar to the doubling of survival in colorectal cancer.[13] For both diseases, the improvement is typically ascribed to "the introduction of new drugs and patient selection based on the recognition that different histological subtypes and driver mutations determine the biology of these malignancies, and predict drug efficacy."[12]

This review examines the evolution of first-line chemotherapy for advanced NSCLC who are not known to harbor a targetable mutation and attempts to quantify the contribution of improved efficacy of first-line chemotherapy to the observed doubling of OS since the introduction of platinum-based regimens in 1977.[16] The impact of other factors that have contributed to improvement of OS in clinical trials are discussed including second-line or third-line therapy, maintenance chemotherapy, performance status (PS) selection, stage migration, sex migration, improved treatment of brain metastases, and better palliative care (Table 2).

HISTORY OF THE EVOLUTION OF CHEMOTHERAPY FOR ADVANCED NSCLC

First-Generation Chemotherapy Regimens (1960–1980s)

The defining characteristic of the first-generation regimens was the use of alkylating agents. In 1948, Karnofsky et al.[17] published one of the first reports evaluating the efficacy of chemotherapy in advanced bronchogenic carcinoma. He reported improvement in symptoms and Karnofsky Performance Score with nitrogen mustard. However, the median duration of benefit was less than a month. In the 1960s, the activity of a number of single agents was explored, such as

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TABLE 1. Metastatic Non–Small-Cell Lung Cancer (NSCLC) Survival Landmarks

Era	Chemotherapy	Median Survival (mo)	One-Year Survival (%)	Two-Year Survival (%)
BSC, 1970–1980		4–5	15	2–3
1st generation, 1970–1980	1960s single agents: 1.Nitrogen mustard 2.Cyclophosphamide 3.Vinblastine 4.Methotrexate 5.doxorubicin 1970s MOPP-like regimens: 1.CAMP[14] 2.MACC[15]	4–5	10–15	2–3
2nd generation, 1980–1995	Cisplatin plus: 1.Vinblastine 2.Vindesine 3.Etoposide 4.Mitomycin 5.Ifosfamide 6.doxorubicin/cyclophosphamide	7	25	6–7
3rd generation, 1995–2005	Cisplatin or carboplatin plus:	8–10	40	12–15
3rd generation, 2005+	1. Vinorelbine 2. Paclitaxel 3. Docetaxel 4. Gemcitabine 5. Pemetrexed	12–13	50–55	20–25

BSC, best supportive care; MOPP, mechlorethamine, vincristine, procarbazine, and prednisone; CAMP, cyclophosphamide, doxorubicin, methotexate, and procarbazine; MACC, methotrexate, adriamycin, cyclophosphamide, and lomustine.

TABLE 2. Reasons Why Survival Has Improved in Advanced Non–Small-Cell Lung Cancer (NSCLC) Clinical Trials

1. Third-generation regimens are slightly better
2. Second-line and third-line chemotherapy
3. Maintenance therapy
4. Performance status selection
5. Stage migration
6. Sex migration
7. Better treatment for brain metastases
8. Better palliative care

cyclophosphamide, vinblastine, and methotrexate. A series of randomized studies from the Veterans' Administration hospitals compared alkylating agents with an inert compound and showed a "slight" favorable effect on survival for nitrogen mustards in squamous cell carcinomas and for cyclophosphamide in small-cell lung cancer.[18] The overall effect on survival was "not remarkable," and a retrospective review of the sixth protocol (nitrogen mustard vs. intravenous cyclophosphamide) showed improvement in the roentgenograms in less than 10% of patients.

In the 1970s, the recognition that mechlorethamine, vincristine, procarbazine, and prednisone chemotherapy could cure Hodgkin lymphoma[19] led to an evaluation of alkylator-based mechlorethamine, vincristine, procarbazine, and prednisone–like regimens in the treatment of lung cancer such as methotrexate, adriamycin, cyclophosphamide, and lomustine[15] and cyclophosphamide, doxorubicin, methotexate, and procarbazine[14] (Table 1). Unfortunately, the trials and meta-analyses of alkylating agents compared with a no chemotherapy arm showed a trend toward a detrimental effect on survival for NSCLC (hazard ratio, 1.26; 95% confidence interval [CI], 0.96–1.66).[20]

Second-Generation Chemotherapy Regimens (1980s–1995)

Second-generation regimens emerged in the mid-1980s based on the addition of a platinum agent combined with companion drugs that included vindesine, vinblastine, etoposide, mitomycin, or ifosfamide. Objective response rates were usually in the range of 20% to 30% with 10% to 20% 1-year survival. These were the first regimens to show a significant improvement in OS and quality of life. In one of the earliest trials comparing cisplatin-based regimens with supportive care, Rapp et al.[5] evaluated cyclophosphamide, doxorubicin, and cisplatin; vindesine and cisplatin; and best supportive care (BSC) in advanced NSCLC population. The median OS of vindesine and cisplatin was 32.6 weeks; 24.7 weeks with cyclophosphamide, doxorubicin, and cisplatin; and 17 weeks with BSC. Of note, many second-generation regimens included alkylating agents like cyclophosphamide and ifosfamide or mitomycin, which have been shown to have a detrimental effect on survival.[20,21]

The best second-generation regimens combined platinum with a plant alkaloid or a podophylotoxin. In 1986, Finkelstein et al.[21] reviewed the extensive experience of the Eastern Cooperative Oncology Group (ECOG) phase III trials. There was no marked differences in outcome among the regimens tested, with a median survival of 23.5 weeks and 1-year survival of 19%. The etoposide–platinum combination had the highest proportion of 1-year survivors at 25%. Because of this effect on survival plus manageable toxicity of this regimen, etoposide plus cisplatin was chosen as the