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50 Years of Progress in the Systemic Therapy of Non–Small Cell Lung Cancer

Heather Wakelee, MD, Karen Kelly, MD, and Martin J. Edelman, MD

OVERVIEW

Non-small cell lung cancer constitutes 85% to 90% of lung cancer and is the most common cause of cancer death. Over the past 50 years, substantial progress has been made in all aspects of lung cancer including screening, diagnostic evaluation, surgery, radiation therapy, and chemotherapy. This review focuses on the advances in systemic therapy during this half century.

Few diseases have engendered as much nihilism as lung cancer. In particular, the role of chemotherapy has frequently been denigrated as toxic and ineffective. However, over the past 50 years remarkable progress has been seen in the treatment of the most common type of lung cancer, non–small cell lung cancer (NSCLC). Platinum-based chemotherapy is clearly established and have demonstrated unequivocal benefit, both in terms of increasing cure rates in adjuvant and multimodality settings in lower stages of disease and enhancing quality and length of life in advanced disease. "Targeted therapies" have emerged in the past decade as effective treatments for advanced disease and are currently undergoing evaluation in lower stages of disease.

ADJUVANT THERAPY

Despite knowledge of an adjuvant chemotherapy benefit in other malignancies, definitive support for this approach in NSCLC was lacking until 2003. Before that time, pooled outcome data and case series from single academic centers were complicated by selection bias, making firm conclusions impossible.

Cisplatin-Based Adjuvant Therapy

A meta-analysis of individual patients published by the Non–Small Cell Lung Cancer Collaborative Group (NSCLCCG) in 1995 reported a negative effect on survival in the earliest adjuvant trials, which used long-term alkylating agent-based regimens, but more promising results with cisplatin-based regimens adopted in the early 1980s.[1] With data from over 1,300 patients enrolled in eight trials of adjuvant cisplatin-based therapy, a trend toward a 5% survival benefit at 5 years was reported (overall survival [OS] hazard ratio [HR] 0.87, 95% confidence interval [CI] 0.74 to 1.02, $p = 0.08$). Multiple randomized phase III trials were launched to confirm these results, although initially with disappointing outcomes (Table 1). The Eastern Cooperative Oncology Group (ECOG) 3590 (Intergroup 0115) study, the European Big Lung Trial (BLT), and the Adjuvant Lung Project Italy (ALPI) were all well-conducted randomized phase III trials of adjuvant cisplatin-based regimens that failed to show a survival benefit with this approach.[2-4] In all three trials, patients with completely resected NSCLC were randomly assigned to approximately 3 months of chemotherapy, initiated within 2 months of surgical resection. Only ALPI was large enough (1,209 patients) to potentially detect a benefit on the order of that seen in the NSCLCCG meta-analysis, yet the OS HR was 0.96 (95% CI; 0.81 to 1.13, $p = 0.589$).[4]

However, in 2003 data from the even larger (1,867 patients) International Adjuvant Lung Cancer Trial (IALT) were presented, with results matching those predicted by the 1995 meta-analysis with a 4% 5-year survival benefit (44.5% vs. 40.4%) and an OS HR of 0.86 (95% CI: 0.76 to 0.98, $p < 0.03$).[5] Patients on this trial were randomly assigned to adjuvant chemotherapy (regimens included cisplatin combined with etoposide, vindesine or vinblastine), with nearly 75% of patients receiving a total of at least 240 mg/m^2 of cisplatin. Enthusiasm was slightly dampened in 2009 when the long-term follow-up results showed an OS HR of 0.91 (95% CI; 0.81 to 1.02, $p = 0.10$), although the disease-free survival benefit persisted (HR 0.88, 95% CI; 0.78 to 0.98, $p = 0.02$).[6]

Other adjuvant chemotherapy trials, initially presented in 2004 and 2005, maintained positive survival benefits even with long-term follow up (Table 1). In contrast to the earlier trials, which used multiple different cisplatin combination regimens including triplets, both the National Cancer Institute of Canada Clinical Trials Group JBR10 trial and the Adjuvant Navelbine International Trialist Association (ANITA) study used a more modern doublet of cisplatin and

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TABLE 1. Cisplatin Adjuvant Trials since 1995 with More than 300 Patients

Trial	N	Overall Survival HR (95% CI)	p value
BLT (Waller 2004)	381	1.02 (0.77-1.35)	0.90
ALPI (Scagliotti 2003)	1,209	0.96 (0.81-1.13)	0.589
IAL (Arriagada 2004; Arriagada 2010)	1,867	0.86 (0.76-0.98); 0.91 (0.81-1.02)	<0.03; 0.10
JBR10 (Winton 2005)	482	0.69 (0.52-0.91)	0.04
ANITA (Douillard 2006)	840	0.80 (0.66-0.96)	0.017

Abbreviations: HR, hazard ratio; CI, confidence interval.

vinorelbine.[7,8] JBR10 enrolled 482 patients with completely resected stage IB-II disease in North America, and with median follow up of 9.3 years has continued to show a significant survival advantage for the adjuvant chemotherapy group compared with observation (HR 0.78, 95% CI; 0.61 to 0.99, $p = 0.04$).[9] The absolute survival benefit at 5 years was 11% in the final analysis. ANITA randomly assigned 840 patients (39% stage IIIA) and reported an OS HR of 0.80 (95% CI; 0.66 to 0.96, $p = 0.017$) with an absolute overall survival benefit at 5 years of 8.6% favoring those who received chemotherapy.

Attempts to reconcile different results from adjuvant trials have led to two large individual patient level meta-analyses (Table 2). The Lung Adjuvant Cisplatin Evaluation (LACE) analysis included 4,584 patients from post-1995 randomized adjuvant cisplatin-based chemotherapy trials whose cohorts were larger than 300 patients: ALPI, IALT, ANITA, BR.10, and BLT.[10] A 5.4% absolute survival benefit at 5 years was reported, corresponding to an OS HR of 0.89 (95% CI; 0.82 to 0.96, $p = 0.005$) in favor of the chemotherapy arm after a median of 5.1 years of follow up. Of note, no benefit was found for stage IA (OS HR 1.41, 95% CI; 0.96 to 2.09) and a borderline benefit was observed for stage IB (OS HR 0.93, 95% CI; 0.78 to 1.10), whereas a significant benefit was achieved for stage II and III with both groups having an OS HR of 0.83 (95% CI; 0.73 to 0.95). The updated NSCLCCG meta-analysis comparison of postoperative chemotherapy included individual data on 8,447 patients and also demonstrated a survival benefit (OS HR 0.86, 95% CI; 0.81 to 0.92, $p < 0.0001$), corresponding to an absolute survival increase of 4% at 5 years (an increase from 60% to 64%; 95% CI 3% to 6%).[11] The concordance of the two meta-analyses supports the current recommendations for adjuvant cisplatin-based chemotherapy after complete resection of stage II and III NSCLC.[12,13]

Controversy continues over the choice of chemotherapy regimen and the utility of predictive markers. Compared to other regimens used in the trials included in the LACE meta-analysis, cisplatin/vinorelbine showed a markedly superior survival benefit but was also associated with toxicity, including febrile neutropenia.[14] In a small phase II adjuvant trial, cisplatin/pemetrexed was better tolerated than cisplatin/vinorelbine but efficacy data were inconclusive.[15] Ongoing phase III trials have included cisplatin/pemetrexed and other modern cisplatin doublets as treatment options, and interim data from the E1505 trial, which closed to accrual in September 2013, revealed that investigators were choosing from among all four chemotherapy options (cisplatin/vinorelbine, cisplatin/gemcitabine, cisplatin/docetaxel, and cisplatin/pemetrexed).[16] Currently, the National Comprehensive Cancer Network (NCCN) guidelines include multiple platinum doublets with known efficacy in advanced stage NSCLC as options for adjuvant therapy of this disease.[17]

KEY POINTS

- Adjuvant platinum-based chemotherapy is the standard of care for node-positive patients with resected disease and strongly considered for patients with tumors 4 cm or larger.
- Concurrent chemotherapy and radiation is the standard of care for fit patients with locally advanced (stage III) NSCLC.
- Platinum-based doublet chemotherapy is the standard of care for fit (PS 0-1) patients with advanced (stage IV) NSCLC and improves both quantity and quality of life in patients without activating mutations. Specific targeted agents produce prolonged progression-free survival in patients with disease characterized by those abnormalities.
- Knowledge of histology (squamous versus nonsquamous) and molecular markers (EGFR, ALK, ROS, RET, etc.) are essential for making appropriate choices for treatment in advanced disease.
- Immunotherapy has substantial promise for the treatment of NSCLC.

Carboplatin Regimens

The role of carboplatin doublets, most notably carboplatin/paclitaxel, remains more controversial. The only randomized adjuvant data for the combination come from the CALGB9633 trial, which included 344 patients with stage IB and was negative in final analysis with an OS HR of 0.83 (90%

TABLE 2. NSCLC Adjuvant Cisplatin Meta-Analyses

Meta-Analyses	N	5-year OS benefit	OS HR (95% CI)	p value
NSCLCCG 1995	1,300	5%	0.87 (0.74-1.02)	0.08
LACE 2008	4,584	5.4%	0.89 (0.82-0.96)	0.005
NSCLCCG 2010	8,447	4%	0.86 (0.81-0.92)	<0.0001

Abbreviations: NSCLC, non-small cell lung cancer; OS, overall survival; HR, hazard ratio; CI, confidence interval.

CI; 0.64 to 1.08, p = 0.125), although the subgroup of patients with tumor size 4.0 cm or greater in diameter did have benefit from the addition of the chemotherapy with an OS HR of 0.69 (90% CI; 0.48 to 0.99, p = 0.043).[18] Despite the lack of data, the use of adjuvant carboplatin/paclitaxel is widespread in the United States, especially in elderly patients.[19]

Oral Agents and Targeted Therapy

In Asia, particularly Japan, oral chemotherapeutics including the combination of uracil and tegafur (a prodrug of 5FU) are used as adjuvant therapy based on multiple positive phase III trials, and more recent studies in that region have explored the use of S-1, an oral agent composed of tegafur and gimeracil.[20] Other oral agents under investigation as adjuvant therapy are the epidermal growth factor receptor (EGFR)-targeted drugs gefitinib and erlotinib. The only randomized adjuvant trial reported to date with an EGFR-targeted agent, JBR.19, was closed early with only 503 patients of a planned 1,242, the majority of whom did not receive the originally planned 2 years of therapy. The results are thus inconclusive but failed to show any benefit with this approach even in the small number of patients whose tumors harbored an EGFR activating mutation.[21] Results from the randomized RADIANT trial of adjuvant erlotinib in patients with tumors with EGFR expression by immunohistochemistry or FISH are anticipated in 2014. However, this trial is unlikely to provide definitive data on this approach for patients with EGFR mutant NSCLC because only approximately 12% of enrolled patients have EGFR activating muations.[22] Enrollment of patients with completely resected early-stage NSCLC with known EGFR mutations or ALK translocations will be coordinated in the United States cooperative group system under the ALCHEMIST umbrella starting in 2014. Under this master protocol patients will be randomly assigned to the appropriate targeted therapy or placebo after resection of tumor and appropriate adjuvant chemotherapy.

Immunotherapy

Accrual to two large phase III adjuvant NSCLC trials of other targeted drugs was recently completed. Results from the MAGRIT trial using a vaccine to MAGE-A3 (a protein found in approximately 35% of resected NSCLCs) are anticipated in 2014 and results from E1505 examining the addition of bevacizumab to adjuvant chemotherapy are expected in 2016.

Molecular-Based Selection of Regimens

Protein expression of ERCC1, a nucleoside excision repair enzyme, is under investigation as a biomarker for cisplatin sensitivity, especially in resected NSCLC. In a retrospective review of the IALT trial, ERCC1 expression was both a prognostic and predictive marker for benefit from adjuvant chemotherapy.[23] However, these results could not be replicated in a later analysis by the same group, bringing into question the utility of the currently available antibody to ERCC1.[24] The French TASTE adjuvant trial was halted on the basis of these results, but the Italian ITACA trial is still recruiting and will provide prospective randomized data about the utility of ERCC1 testing for cisplatin sensitivity, as well as thymidylate synthetase testing as a biomarker for pemetrexed, in the adjuvant setting for resected NSCLC. Multiple other biomarkers with prognostic utility are under investigation, including many interesting gene signature profiles, but prospective randomized data to verify predictive capacity are still lacking.

Adjuvant Radiation Therapy

The use of radiation after resection of stage I and II disease has not been shown to be beneficial, but the utility of this modality in resected stage IIIA disease remains an area of debate and is the subject of an ongoing clinical trial (LUNGART).

Summary and the Next 50 Years

In the past decade adjuvant cisplatin-based chemotherapy has emerged as the standard of care for resected stage II and IIIA NSCLC, with controversy surrounding its efficacy in stage IB disease and use of regimens other than cisplatin/vinorelbine. Targeted therapy and vaccines are under development as adjuvant treatment, with results of phase III trials anticipated in the near future. To date, no predictive markers have proven to be useful, but many hold promise as the field continues to evolve. Future research must also determine whether the benefits of adjuvant therapy after surgical resection of disease will also be validated after nonoperative management (e.g., stereotactic ablative radiotherapy), given the likelihood that the size of this population will increase with increased screening.

LOCALLY ADVANCED DISEASE

Patients diagnosed with locally advanced stage III disease represent a heterogeneous patient population and require multidisciplinary team assessment to determine the optimal treatment regimen. Thoracic radiotherapy (TRT) has been the backbone of treatment for over 50 years. Research conducted in the 1970s established the total dose of 60 Gy that is still in use today.[25]

Radiotherapy Versus Chemoradiotherapy; Sequential Versus Concurrent Chemoradiotherapy

Thoracic radiotherapy alone remained the standard of care for patients with inoperable locally advanced lung cancer until the early 1990s, when two landmark trials incorporating cisplatin-based regimens were reported (Table 3). The first trial by Dillman et al. (CALGB 8433) compared two cycles of cisplatin and vinblastine before TRT versus TRT alone. Patients treated with the combination had a median survival of 13.8 months compared to 9.7 months for the radiotherapy alone arm (p = 0.0066).[26] The second trial evaluated the concurrent administration of daily or weekly cisplatin with TRT versus TRT alone. The daily cisplatin regimen significantly improved survival over radiation alone (p = 0.009).[27] Survival in the weekly cisplatin regimen was intermediate between the two arms and was not significantly different from that of the radiotherapy control arm.

To determine the optimal timing of chemotherapy with radiation, the West Japan Lung Cancer Group evaluated se-

TABLE 3. Selected Trials in Stage III NSCLC

Author	Regimen	N	OS (months)	OS Rate (%)		
				2-year	3-year	5-year
Perez 1980	40 Gy split	93	8.5	-	-	-
	40 Gy	97	10.6	-	-	-
	50 Gy	91	9.5	-	-	-
	60 Gy	84	10.8	-	-	-
Dillman (CALGB) 1990	XRT	77	10	13	11	6
	Chemo→XRT	78	14	26	23	17
Schaake-Koning 1992	XRT	108	46% (1 Yr)	13	2	-
	Daily Chemo+XRT	102	54% (1 Yr)	26	16	-
	Weekly Chemo+XRT	98	44% (1 Yr)	19	13	-
Feruse 1999	Chemo→XRT	158	13	27	15	9
	Chemo+XRT	156	17	35	22	16
Curran (RTOG) 2003	Chemo→XRT	195	15	-	-	10*
	Chemo+XRT	195	17	-	-	16*
Vokes (CALGB) 2007	Chemo+XRT	184	12	29	19	-
	Chemo→Chemo/XRT	182	14	31	23	-
Kelly (SWOG) 2008	Chemo/XRT/Chemo→placebo	118	35**	81	59	-
	Chemo/XRT/Chemo→gefitinib	125	23**	73	46	-
Hanna (HOG) 2008	Chemo+XRT	74	23	-	26	-
	Chemo+XRT→Chemo	73	21	-	27	-
Rigas 2009	Chemo+XRT→placebo	121	27	-	-	-
	Chemo+XRT→erlotinib	122	24	-	-	-
Segawa 2010	Old Chemo+XRT	101	24	48	-	-
	New Chemo+XRT	99	27	60	-	-
Yamamoto 2010	Old Chemo+XRT	153	21	-	-	18
	New Chemo A+XRT	152	20	-	-	18
	New Chemo B+XRT	156	22	-	-	20
Bradley (RTOG) 2011	Chemo+60 Gy	203	29	-	-	-
	Chemo+74 Gy	197	20	-	-	-
Bradley (RTOG) 2013	Chemo+XRT	227	24	-	-	-
	Chemo+XRT+cetuximab	237	23	-	-	-
Butts 2014	Chemo+XRT	410	22	-	-	-
	Chemo+XRT →tecemotide	829	26	-	-	-

Abbreviations: NSCLC, non-small cell lung cancer; OS, overall survival; XRT, radiotherapy; yr, year.
*Reported 2011.
**From Randomization to Gefitinib or Placebo.

quential or concurrent administration of MVP (mitomycin, vindensine, and cisplatin) with TRT. Overall survival was superior in the concurrent arm with a median survival time of 16.5 months versus 13.3 months ($p = 0.03998$).[28] This survival benefit was maintained over time, with a 5-year survival rate of 15.8% versus 8.9%, respectively. In the United States, the Radiation Therapy Oncology Group (RTOG) also showed a survival advantage for the concurrent regimen over sequential therapy.[29,30] In this study (RTOG 9410), concurrent cisplatin plus vinblastine and TRT resulted in median survival of 17 months and a 5-year survival rate of 16% compared to 14.6 months and 10% for chemotherapy followed by TRT ($p = 0.046$). A meta-analysis of six randomized trials addressing chemotherapy timing with radiation revealed a significant increase in OS for concurrent administration of these two modalities (HR = 0.84, 95% CI; 0.74 to 0.95, $p = 0.004$).[31] This survival advantage was the result of improved local regional control (HR 0.77, 95% CI; 0.62 to 0.95, $p = 0.01$). The rates of distant disease progression were similar. However, concurrent therapy was associated with a significantly higher rate of grade 3 and 4 esophageal toxicity of 18%, compared to 4% for sequential therapy ($p < 0.001$). In the United States, two chemotherapy doublets are routinely used in combination with TRT based on phase II data: 1) full-dose cisplatin plus etoposide (PE) for two cycles; and 2) weekly low-dose paclitaxel plus carboplatin (PC).[32-34] A small randomized comparative trial between the PE and PC regimens has been reported.[35] This study found superiority for the PE

regimen; however, the study was underpowered with only 65 patients, and the median survival for both PE (20.2 months) and PC (13.5 months) was inferior to the recently reported results for the control arm (PC) of RTOG 0617 (28.7 months; discussed below). Japanese investigators have conducted two phase III trials comparing concurrent radiation with second and third generation chemotherapy regimens versus their standard regimen of MVP. Efficacy was not superior with the newer agents but hematologic toxicity was lower.[36,37] The added toxicity of concurrent chemoradiotherapy has raised questions as to whether this approach is suitable for elderly patients. Atagi et al. performed a randomized study of concurrent chemoradiotherapy (carboplatin 30 mg/m^2 for the first 20 fractions; 60 Gy) versus radiotherapy alone (60 Gy) in patients aged over 70, which demonstrated a clear advantage for chemoradiotherapy (OS 22.4 months vs. 13.4 months, HR 0.68).[38]

Pemetrexed is the only approved cytotoxic chemotherapy in the post taxane era. Its efficacy and mild toxicity profile, even when combined with platinum agents, suggested that it could be effective and/or less toxic than its cyclic counterpart PE when combined with TRT. In a large randomized phase III trial, patients with locally advanced nonsquamous tumors received either pemetrexed plus cisplatin concurrently with TRT, followed by four cycles of pemetrexed or standard PE and TRT, followed by two cycles of a platinum-based doublet. The trial was halted for futility just shy of completing its enrollment goal of 600 patients. A full analysis of the data is in preparation.

INDUCTION OR CONSOLIDATION CHEMOTHERAPY

Strategies to build on concurrent treatment turned to the delivery of chemotherapy in an induction or consolidation manner. The Cancer and Leukemia Group B (CALGB) evaluated an induction approach using a PC platform. Patients with inoperable stage III disease were randomly assigned to two cycles of full-dose PC followed by weekly low-dose PC with radiation versus weekly low-dose PC and radiotherapy. There was no benefit for induction treatment ($p = 0.3$). Overall survival was low in both arms of the study at 14 months and 12 months, respectively.

SWOG evaluated the consolidation approach in sequential phase II studies examining the addition of two cycles of PE (S9019) and three cycles of docetaxel (S9504) after standard concurrent PE plus radiotherapy. The median survival for patients receiving PE consolidation was low at 15 months, but S9504 showed an unprecedented median survival time of 26 months.[39,40] A randomized phase III trial by the Hoosier Oncology Group (HOG) failed to show a survival benefit for docetaxel consolidation over standard PE with radiation. The median survival was 21.2 months for docetaxel consolidation and 23.2 months for observation ($p = 0.883$).[41]

The role of consolidation may be dependent on the chemotherapy regimen used during concurrent chemoradiotherapy. Both the SWOG and HOG regimens use "full-dose" chemotherapy whereas others use low-dose or radiosensitizing chemotherapy. The recent results of RTOG 0617 support the common practice of two cycles of full-dose PC (P, 200 mg/m^2; C, area under the curve = 6) after weekly PC and radiation to eradicate micrometastatic disease.

Anti-EGFR and Anti-VEGF

The discovery of EGFR tyrosine kinase inhibitors (TKIs) with their convenient oral daily dosing and low toxicity profile provided ideal agents for evaluation as maintenance therapy. Building on their consolidation strategy, SWOG launched a randomized trial to determine the role of maintenance gefitinib (S0023) in patients with locally advanced disease. Patients with nonprogressing disease who received PE plus TRT followed by docetaxel were randomly assigned to gefitinib or placebo for 2 years. An unplanned interim analysis conducted after the failure of gefitinib to show a survival benefit over placebo in previously treated patients with advanced disease revealed an inferior survival outcome for patients assigned to gefitinib (HR 0.633, 95% CI; 0.44 to 0.91; $p = 0.013$).[42,43] An additional phase III trial evaluating erlotinib after concurrent chemoradiotherapy did not meet its primary progression-free survival (PFS) endpoint.[44]

Redesigning the definitive chemoradiation regimen by incorporating novel agents and/or radiation schema has also been investigated. Like cytotoxic chemotherapy, molecularly targeted agents have been shown to be radiosensitizers. In a single arm phase II study of cetuximab in combination with concurrent PC and TRT (RTOG 0324), a favorable OS of 22.7 months led RTOG to revise its randomized phase III trial evaluating 74 Gy versus 60 Gy to include an evaluation of cetuximab.[45] Survival was poorer with the higher radiation dose (HR 1.56, 95% CI; 1.19 to 2.06, $p = 0.0007$) and there was no survival advantage for the addition of cetuximab (HR 0.99, 95% CI; 0.78 to 1.27, $p = 0.48$).[46-48] The VEGF inhibitor bevacizumab showed efficacy in combination with chemotherapy for patients with stage IV disease with nonsquamous cell histology that justified its evaluation in stage III patients. Unfortunately, evaluation of bevacizumab was short-lived, with several phase II trials showing high rates of pulmonary bleeding and tracheoesophageal fistula formation that resulted in early study closures.[49,50]

Immunotherapy

Exploiting the immune system to assist in tumor destruction has become a promising area of therapeutic evaluation in lung cancer. One approach is vaccine therapy. Tecemotide is a mucin 1 antigen-specific vaccine that induces a T-cell response. Preliminary data suggested a benefit in patients with stage III disease after chemoradiotherapy;[51] however, the START randomized phase III trial did not show an overall survival advantage with the vaccine (HR 0.88, 95% CI; 0.75 to 1.03, $p = 0.123$). Interestingly, a survival benefit was observed in the large subset of 538 patients who received concurrent chemoradiation (HR 0.78, 95% CI; 0.64 to 0.95, $p = 0.016$).[52] A confirmatory trial in this population is planned.

The Next 50 Years

In summary, multiple strategies to improve on concurrent chemoradiotherapy have been unsuccessful. In the United States, cyclic PE or weekly PC plus 60 Gy of TRT remains the standard of care. Future studies are focusing on the integration of molecularly targeted agents in appropriate patient populations. For example, RTOG and the Alliance have recently launched a randomized phase II trial for patients with EGFR-mutated or ALK-positive tumors. Patients will be randomly assigned to 3 months of erlotinib or crizotinib, respectively, followed by chemoradiotherapy versus chemoradiotherapy alone (ClinicalTrials.gov identifier, NCTO1822496). The primary study endpoint is PFS. Radiation strategies under investigation include evaluation of hypofractionation, stereotactic radiotherapy boosts, proton therapy, and adaptive radiotherapy using changes in tumor volume to adjust the TRT treatment plan during therapy.

Over the past 50 years steady progress has been made in the treatment of locally advanced lung cancer. Survival times have more than doubled and toxicity has decreased. Although still a treatment challenge, we are optimistic that, with the increasing number of efficacious molecularly targeted agents accompanied by advances in technology, we could see substantial improvement in long-term survival and cure rates.

ADVANCED NSCLC

Although advanced NSCLC is incurable with current therapeutic options, it is clear that there has been measurable progress over the past 5 decades. It is remarkable that only 20 years ago there was still discussion regarding the validity of treatment for any patient with advanced NSCLC, whereas today we have unequivocally established the value of treatment for essentially all fit patients with advanced disease, including second- and third-line treatments.

Chemotherapy versus Best Supportive Care

Limited efficacy, significant toxicity, and the poor initial performance status of many patients raised questions regarding the utility of chemotherapy in patients with advanced NSCLC. Even into the 1990s and later, there was debate as to whether chemotherapy of any type is advantageous. However, a number of studies have clearly demonstrated that platinum-based chemotherapy improves overall survival and quality of life compared to best supportive care (BSC)[1,53-55] (Table 4). Cartei et al. demonstrated a substantial survival advantage (8.5 vs. 4.0 months, $p < 0.0001$) for treatment with cisplatin/cyclophosphamide/mitomycin versus BSC. Rapp reported an NCI-Canada trial that compared two chemotherapy regimens (vindesine/cisplatin and cyclophosphamide/doxorubicin/cisplatin) to each other and to BSC, and found that the chemotherapy regimens were nearly equivalent and superior to BSC.[56] Cullen evaluated the mitomycin/ifosfamide/cisplatin regimen versus BSC or radiotherapy. In both studies, there was an advantage in terms of survival and quality of life with chemotherapy. Quality of life was evaluated using the instrument EORTC QLQ-LC13, which involves questions assessing symptoms and toxicity, coughing, breathlessness (at three different exercise levels), hemoptysis, pain, appetite, anxiety, depression, dysphagia, nausea, and malaise. There was a noticeable advantage with chemotherapy in both trials. These findings are all the more remarkable given that many trials were performed using cisplatin, an agent known for its substantial toxicity, in the era before effective antiemetic prophylaxis with serotonin antagonists. The fact that objective testing of quality of life favored treatment is testimony to both the toxicity of the disease and the efficacy of platinum-based therapy.

Single-Agent Cisplatin versus Combinations with New Drugs of the 1990s

By 1990, consensus had emerged that platinum-based therapy was superior to best supportive care for patients with good performance status, i.e., ECOG score 0–1. There was, however, considerable debate over whether there was an advantage to combining platinum with other drugs. ECOG 1583 evaluated single agents followed by combination therapy versus combination therapy and demonstrated that combinations might be superior in terms of response rate, but not in terms of survival, compared to single agent platinum.[57] At that time several new agents with single agent activity in advanced NSCLC emerged, in particular vinorelbine, paclitaxel, docetaxel, gemcitabine, and irinotecan. Vinorelbine became the first agent licensed in lung cancer after a comparative trial versus 5-fluoruracil/leucovorin demonstrated an advantage for vinorelbine (30 weeks vs. 22 weeks, $p = 0.03$).[58] This led to trials to evaluate these new drugs in combination versus cisplatin alone. Trials testing this strategy uniformly demonstrated an advantage in terms of overall survival for the combinations.[59,60]

Comparison of Doublet Regimens

The major question by the mid 1990s was whether any of the new regimens were superior to the others (Table 4). Two major U.S. cooperative group studies, SWOG 9509 and ECOG 1594, addressed this question. SWOG tested cisplatin/vinorelbine versus carboplatin/paclitaxel whereas ECOG evaluated two different paclitaxel regimens (cisplatin/paclitaxel and carboplatin/paclitaxel) versus cisplatin/docetaxel and cisplatin/gemcitabine.[61,62] Both trials reached the same conclusion: that the regimens were equivalent. There was a remarkable uniformity in the outcomes, with all regimens demonstrating an approximately 8-month median OS and 1-year survival of approximately 35%. These studies established the benchmarks for outcomes in NSCLC for the next decade. A number of other studies using a variety of regimens reached the same conclusion. Although commonly regarded as negative trials, they in fact established that there were a number of alternative agents that resulted in similar outcomes and provided the foundation for a number of trials (to date unsuccessful) exploring the possibility of inproved selection of agents based on biologic characteristics. In addi-

TABLE 4. Selected Trials in Advanced NSCLC: First-Line Chemotherapy

Study	N	Regimens	RR (%)	OS (mo)	1-year (%)	2-year (%)
Rapp/NCI-Canada (1988)	150	VP	25.3	7.5		
		CAP	15.3	5.7		
		BSC		4.1		
				(p = 0.02)		
Cartei (1993)	102	Cisplatin/cyclophosphamide/MMC		8.5	39	
		BSC		4.0		
				(p <0.0001)		
Cullen (1999)	351	MIC		6.7		
		BSC		4.8		
				(p = 0.03)		
Crawford (1996)	216	Vinorelbine	12	6.9	25	
		5FU/leucovorin	3	5.1	16	
				(p = 0.03)		
Kelly/SWOG (2001)	408	Cisplatin/vinorelbine	28	8	36	16
		Carboplatin/paclitaxel	25	8	38	15
Schiller/ECOG (2002)		Cisplatin/paclitaxel	21	7.8	31	10
		Cisplatin/gemcitabine	22	8.1	36	13
		Cisplatin/docetaxel	17	7.4	31	11
		Carboplatin/paclitaxel	17	8.1	34	11
Gridelli (2003)	501	Gemcitabine/vinorelbine	25	7.4	31	
		Cisplatin/vinorelbine or gemcitabine	30	8.8	37	
Kosmidis (2002)	509	Carboplatin/paclitaxel	28	10.4		
		Gemcitabine/paclitaxel	35	9.8		
Scagliotti (2008)	1,669	Cisplatin/gemcitabine		10.3	41.9	14
		Cisplatin/pemetrexed		10.3	43.5	18.9
Ciuleanu (2009)	663	Platinum therapy × 4 → pemetrexed	N/A	13.4		
		Platinum-based therapy × 4		10.6		

Abbreviations: NSCLC, non-small cell lung cancer; RR, response rate; OS, overall survival; BSC, best supportive care. VP, vinblastine, cisplatin; CAP, cyclophosphamide, adriamycin, cisplatin; MMC, mitomycin C; MIC, mitomycin, ifosfamide, cisplatin; 5FU, 5-fluorouracil.

tion, there were marked differences in potential toxicities (e.g., neuropathy) with different agents, as well as in drug schedule and expense. Therefore, on a day-to-day basis, treatment could be individualized based on these features.

Following the demonstration of benefit for these new agents, the question of combining them with the goal of avoiding platinum agents and their associated toxicities yielded a number of trials. These studies demonstrated the feasibility of the approach but no advantage in terms of either toxicity or survival, and this approach has largely been abandoned.[63]

Second-Line Chemotherapy

At the same time as the question of the optimal first-line doublet therapy was being addressed, a previously unheard of concept emerged—that chemotherapy might be efficacious in the second-line setting. As noted previously, there was still vigorous debate regarding the value of initial chemotherapy, even in patients with good performance status, well into the 1990s. Two trials with docetaxel, one comparing the drug (at two different dose levels) versus a "dealer's choice" of either ifosfamide or vinblastine (TAX 320) and the second comparing docetaxel (also with two different dose levels) versus BSC, led to approval of single agent docetaxel as second-line therapy for advanced NSCLC based on survival advantage[64,65] (Table 5). This was followed by a trial that evaluated pemetrexed versus docetaxel in the second line setting. Although designed to demonstrate superiority, the trial demonstrated similar efficacy in terms of survival but improved tolerability, and led to U.S. Food and Drug Administration (FDA) approval.[66] An NCI-Canada trial evaluated erlotinib compared with placebo in the second- and third-line settings and showed superiority in terms of survival. Therefore, by the early 2000s three agents had demonstrated a small, but real, improvement in overall survival in the second-line, and even third-line, settings of advanced NSCLC.

The Re-Emergence of Histology

With the advent of flexible bronchoscopy, computed tomography (CT)-directed biopsies, and the increasing use of fine needle aspiration for diagnosis of malignancy, the only relevant question raised by practitioners was whether a patient

TABLE 5. Selected Trials: Second-Line Chemotherapy

Study	N	Regimens	RR	OS (mo)	1-yr (%)
Fosella (TAX 320) (2000)	373	Docetaxel (75)	6.7	5.7	32
		Docetaxel (100)	10.8	5.5	21
		Ifosfamide or vinorelbine	0.8	5.6	19
Shepherd (2000)	203	Docetaxel (75)	7	7.5	37
		Docetaxel (100)	7	5.9	19
		BSC	0	4.6	19
Hanna (2004)	571	Pemetrexed	9.1	8.3	29.7
		Docetaxel	8.8	7.9	29.7

Abbreviations: RR, response rate; OS, overall survival.

had small cell or non–small cell lung cancer. As all variants of the latter (e.g., adenocarcinoma, squamous cell carcinoma) were treated in a similar manner, there seemed no point in expending additional effort either at the time of biopsy or by the pathologist in subdividing the disease. However, clinical observations of toxicity associated with bevacizumab and squamous cell carcinoma and efficacy associated with pemetrexed in nonsquamous carcinomas, both in the first-line setting, renewed the importance of making an accurate histologic diagnosis.

In a randomized phase II trial Johnson et al. evaluated bevacizumab at different dose levels in combination with carboplatin/paclitaxel. In addition to observing a promising level of activity, which was ultimately confirmed in the ECOG 4599 trial, they also noted six episodes of massive hemoptysis, four of which were fatal.[67,68] All of these cases occurred in patients with squamous cell carcinoma and resulted in the exclusion of those patients from the definitive trial (E4599) that led to approval. The E4599 study demonstrated significantly superior survival (12.3 vs. 10.3 months, $p = 0.003$) for carboplatin/paclitaxel/bevacizumab versus carboplatin/paclitaxel. However, the role of bevacizumab is complicated by the inability of a large European trial to confirm the benefit of adding bevacizumab to the cisplatin/gemcitabine regimen[69] (Table 6).

The importance of histology was affirmed in a more positive manner with pemetrexed. Retrospective data led to a planned subgroup analysis by histology in a randomized trial of cisplatin/gemcitabine versus cisplatin/pemetrexed that demonstrated an advantage for the pemetrexed arm for nonsquamous carcinoma (adenocarcinoma: 12.6 vs. 10.9 months, $p = 0.03$; large cell carcinoma: 10.4 vs. 6.7 months, $p = 0.03$). Conversely, there was a superior survival for patients with squamous carcinoma receiving gemcitabine-based therapy (10.8 vs. 9.4 months, $p = 0.05$).[70]

Interestingly, this seemingly basic issue remains somewhat muddled as there is marked discordance among pathologists over making clear-cut diagnoses based on surgical specimens and none of the studies demonstrating the importance of histology actually relied on commonly used histochemical tech-

TABLE 6. Selected Trials: Chemotherapy +/− "Targeted Agents"

Study	N	Regimens	RR	OS (mo)	1 yr (%)	2 yr (%)
Sandler/ECOG	878	Carboplatin/Paclitaxel	15	10.3	51	23
		Carboplatin/Paclitaxel/Bevacizumab	35	12.3	44	15
Reck 2010	1,043	Cisplatin/Gemcitabine	21.6	13.1		
		Cisplatin/Gemcitabine/Bevacizumab (7.5)	37.8	13.6		
		Cisplatin/Gemcitabine/Bevacizumab (15)	34.6	13.4		
Giaccone (INTACT-1)	1,093	Cisplatin/Gemcitabine	49.7	9.9	44	
		Cisplatin/Gemcitabine/Gefiitinib500	50.3	9.9	43	
		Cisplatin/Gemcitabine/Gefitinib250	44.8	10.9	41	
Herbst (INTACT-2)	1,037	Carboplatin/Paclitaxel	28.7	9.9	42	
		Carboplatin/Paclitaxel/Gefitinib500	30	8.7	37	
		Carboplatin/Paclitaxel/Gefitinib250	30.3	9.8	41	
Herbst (TRIBUTE)	1,059	Carboplatin/Paclitaxel	19.3	10.5		
		Carboplatin/Paclitaxel/Erlotinib	21.5	10.6		
Gatzmeir (TALENT)	1,172	Cisplatin/Gemcitabine	29.9	44.1 wks	42	
		Cisplatin/Gemcitabine/Erlotinib	31.5	43 wks	41	

Abbreviations: RR, response rate; OS, overall survival; wks, weeks; mo, months; yr, year.

niques to differentiate problematic cases.[71] The need for specimens adequate to make a firm histologic diagnosis dovetailed with the need for larger specimens for DNA isolation and FISH analysis in the emerging era of molecularly targeted agents.

The Molecular Era

The success of bevacizumab discussed above ushered in the molecular era of chemotherapy; that is, the use of agents with targets other than DNA or tubulin. The other agents that inaugurated this era, and somewhat inadvertently went one step further to personalized therapy, were the EGFR inhibitors gefitinib and erlotinib. Although four randomized trials with these agents combined with chemotherapy were negative, the results for erlotinib versus placebo in second- or third-line therapy (see above), coupled with anecdotal reports of dramatic responses in some heavily pretreated patients, kept the agent under consideration[72-76] (Table 6). These patients were overwhelmingly characterized by a never or scant smoking history and seemed to be more frequently of female gender and Asian ethnicity. Two groups in Boston ultimately discovered the reason for these responses: specific activating mutations in the internal domain of EGFR.[77,78] The next key question was whether these agents could be used as initial therapy. The Iress PanAsia Study (IPASS) was the first to address this issue.[79] The trial commenced before the clear identification of the EGFR mutation and selection was based on smoking status, with eligible patients required to be never or scant smokers. The trial demonstrated superior PFS for gefitinib over platinum-based chemotherapy, but no OS advantage. Importantly, tumor specimens were submitted for many of the patients and molecular analysis could be performed. This analysis conclusively demonstrated that patients whose disease was characterized by EGFR mutations had substantial benefit (in terms of PFS) whereas those who did not have EGFR mutations did not benefit from gefitinib and are most appropriately treated with chemotherapy, irrespective of smoking status. Since IPASS, six trials have selected patients based on EGFR mutation for treatment with platinum-based chemotherapy versus EGFR TKI[80-87] (Table 7). All have demonstrated superior PFS for the EGFR TKI, but none have demonstrated an OS advantage because of cross over effects. With success has come the identification of resistance to EGFR TKIs, most notably the T790M mutation in EGFR and Met amplification. At the present time, the next generation of EGFR TKIs is entering trials. These agents are distinguished by the fact that they were designed to inhibit the mutated receptor, most particularly the T790M mutation, and preliminary results demonstrate activity in patients who have progressed on prior TKIs and substantially less cutaneous toxicity.[88]

The discovery of the EGFR mutation prompted studies to find other activating mutations. This search was rewarded with the identification of the ALK activating translocations.[89] Fortuitously, crizotinib, already under development as an inhibitor for c-met, was known to be active against ALK and populations were quickly enriched for ALK translocations. This became the first example in lung cancer where early-phase drug development was successfully directed by a biologic variable. Consequently, approval came rapidly and second-generation agents that are designed specifically for activated ALK and address resistance mechanisms are now in trials.

The past 24 months have witnessed a marked improvement in our knowledge of activating mutations with the identification of a number of actionable abnormalities that have been validated with anecdotal use of existing agents or early trials with enriched populations. These abnormalities include Ret, Ros, and B-raf.[90-92] However, no agent is currently available that targets the most common (and first discovered) genetic abnormality in NSCLC, k-ras mutations, although recent studies indicate the feasibility of small molecule inhibitors.[93]

The Other 85%

The substantial progress in the identification of activating mutations and translocations has tended to overshadow the fact that the overwhelming majority of patients do not have actionable mutations. In addition, as can be seen in Table 7, the dramatic and occasionally durable responses seen with the newer agents obscures the underlying reality that the median duration of response is less than 1 year and the median overall survival is approximately 30 months. Virtually all patients with advanced disease will be considered for chemotherapy at some point in their illness. Attempts to personalize chemotherapy based on molecular markers, including ERCC1, RRM1, and beta tubulin, have not been fruitful despite substantial preclinical data.[94-96] Great effort has been expended in evaluating the prolonged use of single agents including pemetrexed, gemcitabine, and taxanes.[97-100] Positive results of this maintenance therapy approach in terms of

TABLE 7. Chemotherapy versus EGFR TKIs in Patients with EGFR-Mutated Tumor

Study	Treatment	N	Median PFS (months)	Median OS (months)
Maemondo	Gefitinib versus carboplatin/paclitaxel	230	10.8 versus 5.4 ($p < 0.001$)	30.5 versus 23.6 ($p = 0.31$)
Mitsudomi	Gefitinib versus cisplatin/docetaxel	177	9.2 versus 6.3 ($p < 0.0001$)	36 versus 39 HR 1.19
OPTIMAL	Erlotinib versus carboplatin/gemcitabine	165	13.1 versus 4.6 ($p < 0.0001$)	HR = 1.065 ($p = 0.65$)
EURTAC	Erlotinib versus platinum-based chemotherapy	174	9.7 versus 5.2 ($p < 0.0001$)	19.3 versus 19.5 ($p = 0.87$)
LUX-Lung 3	Afatanib versus CDDP/Pemetrexed	345	11.1 versus 6.9 ($p < 0.0004$)	Not reported
LUX-Lung 6	Afatanib versus gemcitabine/CDDP	364 (2:1)	11.0 versus 5.6 ($p < 0.0001$)	HR = 0.95 ($p = 0.76$)

Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; PFS, progression-free survival; OS, overall survival; CDDP, cisplatin.

overall survival with pemetrexed have been seen, but may represent an artifact of trial design.[101]

The last 2 years have seen the most surprising development for the treatment of advanced disease, the advent of immunotherapy. Although there were early reports of benefits of immunologic therapies, these were rarely beyond the level of anecdote. Ipilumamab, approved for therapy in melanoma, appeared to provide some benefit in addition to standard chemotherapy in a randomized phase II study.[102] More remarkably, there are reports of activity of anti-PD1 and PD-L1 antibodies with substantial and occasionally durable responses in patients with heavily pretreated disease.[103,104]

The Next 50 Years

Although we can envision a time when tobacco use has been eradicated or at least substantially reduced, which will markedly reduce the incidence of lung cancer, it is unlikely that the lung cancer epidemic will abate in the next several decades. In fact, an increase in tobacco use, in addition to severe industrial pollution, in emerging nations and particularly Asia, has been accompanied by a dramatic increase in lung cancer in those regions. Furthermore, lung cancer in individuals who never or hardly ever used tobacco will remain an important disease entity.

Much of the recent progress in systemic therapy has come through defining subsets and active agents in the nonsquamous (predominantly adenocarcinoma) subgroup. Recent research has identified new potential targets in squamous cell carcinoma, a common subset of NSCLC.[105] For example, fibroblast growth factor receptor (FGFR) abnormalities are common in squamous cell cancer (more than 20% of cases) and trials of FGFR inhibitors are currently in progress. Of note, there is some evidence that this histology may be sensitive to anti-EGFR antibody therapy combined with chemotherapy and that this benefit is dependent on EGFR expression as determined by immunohistochemistry.[106] Immunotherapy, specifically the anti-PD1/PD-L1 therapies, hold the promise of significant advances in all stages of disease. The notable efficacy of pathway targeted agents in advanced disease has led to studies in the adjuvant setting and as part of the chemoradiation strategy for locally advanced disease.

In summary, the combination of reduced tobacco abuse, effective screening strategies, and improved systemic therapy hold the real promise of a substantial reduction of morbidity and mortality from NSCLC in the next decade and certainly within the next 50 years.

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Relationships are considered self-held and compensated unless otherwise noted. Relationships marked "L" indicate leadership positions. Relationships marked "I" are those held by an immediate family member; those marked "B" are held by the author and an immediate family member. Relationships marked "U" are uncompensated.

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