

Second-Line Chemotherapy and Beyond for Non- Small-Cell Lung Cancer

Abstract

Platinum-based chemotherapy is now established in the treatment of all stages of lung cancer. Despite the benefits of therapy, the majority of patients treated for lung cancer will ultimately progress. Some will retain good performance status and be candidates for additional, tumor-directed treatment. Docetaxel and pemetrexed have documented activity in phase III trials in patients progressing after first-line, platinum-based therapy. Gefitinib has recently been approved for treatment of disease in the third line. Numerous other agents with diverse mechanisms are currently undergoing evaluation in this setting. This review evaluates the population eligible for such treatments and discusses recent trials in second and subsequent lines of therapy.

Keywords

Docetaxel, pemetrexed, gefitinib, erlotinib, bexarotene, bevacizumab

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Introduction

In the United States, lung cancer remains the leading cause of cancer-related death for both men and women, with more than 154,000 deaths in 2002, representing 28% of cancer-related mortality.¹ Treatment of patients with metastatic disease with chemotherapeutic agents introduced in the 1990s combined with platinum agents has resulted in median survivals of 8–10 months and 30–40% of patients alive at 1 year.^{2–5} For the first time, a substantial portion of patients (10–15%) are surviving for 2 years.

A consequence of this (albeit limited) success has been the clinical situation in which a patient with advanced disease experiences progression after a first-line chemotherapy regimen yet maintains an adequate performance status and desires additional treatment. Adding to this population are patients who have progressed after having multimodality therapy for stage III disease as well as patients who have received adjuvant chemotherapy for stage I and II disease. This growing population of patients is clearly heterogeneous, and it is likely that different treatment approaches will emerge based upon the timing of relapse and the nature of prior therapy. There have been numerous developments since this topic was reviewed by Huisman et al.⁶

Timing of Relapse: Recurrent Versus Refractory

Lessons from other malignancies are instructive. An early observation in Hodgkin lymphoma was that patients who had responded to chemotherapy were likely to respond to further therapy (or even the same treatment) if enough time had elapsed. In small-cell lung cancer, similar findings have been reported.⁷ Though the data are less robust, it is clear that patients with progressive non-small-cell lung cancer (NSCLC) can be classified into at least 2 different groups based upon the timing of progression. Those who progress within 6 months of prior therapy (and particularly those who progress while actually receiving therapy) can be termed refractory. Patients who progress 6 months or more after prior therapy are more likely to respond to subsequent treatments. There are essentially no data on rechallenge using the same agents. There is also relatively little data on the degree to which prior response predicts for outcome of second-line treatment.

The Nature of Prior Therapy

Most studies of second-line therapy have been predicated on the assumption that first-line treatment consisted of a platinum-based regimen. While this is frequently the case, there has been growing interest in the use of nonplatinum regimens. The enthusiasm for these regimens has been tem-

pered somewhat by the results of multiple randomized trials demonstrating that these regimens are neither more effective nor less toxic than standard therapy. Nevertheless, there is still some interest in single, nonplatinum agents in elderly or poor performance status (PS) patients. There are essentially no data on the use of platinum-based regimens after progression on nonplatinum therapies, although there is anecdotal evidence of responses.

Rarely considered is the clinical context of second-line therapy—specifically, whether the therapy is second-line after progression in de novo metastatic disease or progression after treatment of earlier-stage disease in which chemotherapy was employed with curative intent. In addition, there will be a growing fraction of patients for whom second-line therapy is used after adjuvant therapy administered in the postoperative setting. These groups are likely to represent very distinct subsets in terms of inherent disease biology, as well as general fitness for second and subsequent treatments.

Other Factors Relating to Second-Line Therapy

The population of patients receiving second-line chemotherapy for NSCLC is highly selected. In addition to surviving, the patients entered into clinical studies of second-line therapy must have maintained reasonable PS (ie, PS 0–2). Other factors also appear to predict for selection to receive second-line therapy. In a retrospective study of second-line therapy, nonsquamous histology, female sex, and good baseline PS predicted for treatment. Patients who had received fewer than 4 cycles of first-line therapy were much less likely to receive second-line treatment. Overall, less than 50% of patients underwent second-line treatment.⁸

Docetaxel in Second-Line Therapy

The first agent approved in the second-line treatment of NSCLC was docetaxel (Table 1). A National Cancer Institute of Canada (NCIC) trial compared docetaxel 75 mg/m² or

100 mg/m² versus best supportive care. This trial found superior quality of life and, for the 75 mg/m² patients, length of life as well.⁹ An industry-sponsored study in the United States compared docetaxel at either 75 mg/m² or 100 mg/m² versus a physician's choice of either vinorelbine or ifosfamide. Quality of life and survival were again superior for docetaxel at 75 mg/m².¹⁰ The concordant results of these 2 trials lend strength to the conclusion that docetaxel at 75 mg/m² every 3 weeks has a clear role in this setting. Of note, this advantage was seen even for patients with prior paclitaxel therapy. Importantly, no patient who progressed on prior platinum therapy responded to docetaxel. In the US trial, there was a trend towards higher response rate and possibly better survival for patients who had responded to prior platinum therapy.

Despite the advantages of docetaxel, there are still significant questions regarding its use. First, though 75 mg/m² was clearly better tolerated than 100 mg/m², it is still a drug with significant toxicities (including fatigue and myelosuppression). A weekly schedule (35 mg/m²) may be better tolerated, but recent data indicate that this approach may be less effective. Three trials presented in 2003 evaluated weekly docetaxel versus every 21 days. By most criteria, these trials demonstrated superior tolerability in terms of hematological toxicity, alopecia, and pain control. However, in the German randomized study (N=213), 32% of patients undergoing therapy with docetaxel 75 mg/m² every 21 days received 4 or more cycles of therapy versus only 8% of patients receiving docetaxel 35 mg/m² weekly, 3 out of 4 weeks.¹¹ This implies a longer time to treatment progression.

A second, Spanish trial (n=179) included an almost identical evaluation (docetaxel 75 mg/m² every 21 days versus weekly docetaxel 36 mg/m² 6 out of 8 weeks). Median survival favored the every-21-day arm (7.1 months vs 5.1 months, *P*<.05).¹² In this study, diarrhea and oral mucositis (grade 1/2) were higher with weekly administration. A third, Italian study included a similar evaluation (docetaxel 75 mg/m² every 21 days vs docetaxel 33.3 mg/m² 6 out of 8 weeks) and found equivalent survival and global quality of life but advantages for the weekly schedule in terms of cognitive function, pain, cough, and hair loss. In addition, there was less neutropenia and febrile neutropenia, but more diarrhea for the weekly versus every-3-week regimen.¹³ All of these reports represent preliminary data, and the final conclusions are pending. However, these results should suggest caution in adopting the weekly schedule for routine use. Additionally, docetaxel has now received approval for first-line use, and the population of patients who are docetaxel-naïve in second line is decreasing.

Attempts to improve treatment outcomes by combining docetaxel with other agents have also been unrewarding to date. A trial combining docetaxel with irinotecan was inferior to docetaxel alone, with inferior response and increased toxicity.¹⁴

Table 1. Results of Phase III Trials in Second-Line Therapy

Regimen	Docetaxel vs Vinorelbine or Ifosfamide		Docetaxel vs BSC		Docetaxel vs Pemetrexed	
	D	V/I	D	BSC	D	P
Number evaluable	125	123	104	100	288	283
% refractory	24	32	ns	ns	48	50
% prior taxane	42	41	0	0	28	26
RR	6.7	0.8	5.8	0	8.8	9.1
RR (refractory)*	5	0	0	0	ns	ns
TTP	2.1	1.9	2.4	1.5	2.9	2.9
MST	5.7	5.6	7	4.6	7.9	8.3
1-year survival	32	19	29	19	30	30

BSC=best supportive care; ns=not stated; RR=response rate; TTP=time to progression; MST=median survival time.

*Platinum-refractory defined as progression within 6 months of therapy.

Table 2. Recently Completed Phase II Trials in Second-Line Therapy

Agent	Class	Design	Number	Response rate, %	Median survival, mo	1 year survival, %
Cryptophycin	Anti-tubulin	Phase II	25	0	4.1	0
BMS 247550	Anti-tubulin (epothilone)	Randomized phase II	76	13	7.5	36
Paclitaxel (weekly)	Anti-tubulin (taxane)	Phase II	62	8	5.2	20
BMS-184476	Anti-tubulin (taxane)	Phase II	51	15.6	NS	NS
ZD0473	Platinum	Phase II	21 (resistant) 18 (sensitive)	0 0	NS NS	15.7 22
Toremifene modulated platinum	Platinum	Phase II	28	18	8.1	30
Pivanex	Butyrate	Phase II	47	4.3	7.3	24

NS=not stated.

Pemetrexed

Pemetrexed (Alimta, Lilly), a new antifolate agent with demonstrated activity in mesothelioma, has been tested in the second-line therapy of NSCLC. A phase III trial randomizing patients between pemetrexed (500 mg/m² every 21 days with B₁₂ and folate supplementation) and docetaxel (75 mg/m² every 21 days) demonstrated a similar level of activity but superior tolerability.¹⁵ There was considerably less myelotoxicity and alopecia. Significantly fewer patients required hospitalization with pemetrexed compared with docetaxel. Activity in terms of response rate and median and 1-year survival are superimposable on the results obtained for docetaxel (Table 1). The drug has recently become available in the United States.

Gemcitabine in Second-Line Therapy

Another agent with probable second-line activity is gemcitabine (Gemzar, Lilly). Several phase II experiences in the United States and Europe appear comparable to the level of activity demonstrated by docetaxel.¹⁶ However, there are no phase III data confirming these studies. Some have combined gemcitabine with other agents, most notably vinorelbine in this setting.¹⁷ The results are not significantly different from those reported with gemcitabine as a single agent. Furthermore, it is difficult to understand what vinorelbine (Navelbine, GlaxoSmithKline), a drug without activity in second-line therapy, would add in such a regime. In vitro evidence for this combination demonstrates additivity at best, and more likely antagonism.¹⁸ A randomized trial comparing gemcitabine/vinorelbine to either agent alone in first-line therapy demonstrated no advantage for the combination.¹⁹

Third-Line Therapy

While second-line treatment for advanced NSCLC was considered *avant garde* a decade ago, the idea of third-line therapy in any significant population of patients was considered truly absurd. Remarkably, an increasing population of patients is emerging for whom this option needs to be considered.

Gefitinib (Iressa, AstraZeneca) is the first drug to receive approval for this indication. This approval was controver-

sial as the basis for this approval was response rate in third line therapy. The drug had previously failed to demonstrate benefit as first-line treatment when combined with standard therapy.^{20,21}

Two large phase II trials of gefitinib monotherapy, Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL) 1 and 2, evaluated the agent in pretreated NSCLC. IDEAL 1 also looked at the safety profile, while IDEAL 2 sought to evaluate symptom improvement as an additional primary endpoint.^{22,23} The response rate was 19% in IDEAL 1; IDEAL 2 used dosages of 250 mg/day and 500 mg/day, with response rates of 12% and 9%, respectively. Many patients, even those with poor PS, experienced symptom improvement within 2 weeks of starting gefitinib treatment. This improvement in quality of life scales, though questionable as there was no randomization against either supportive care or another agent, was the major impetus for granting conditional approval to market the agent in the United States. Approval was granted under the provision that appropriate randomized trials be conducted.

Subset analysis appears to demonstrate that female sex, adenocarcinoma (in particular, bronchoalveolar histology), and nonsmoking status were predictors of response.^{23,24} Female sex was a particularly strong predictor in both IDEAL trials. In the primarily North American IDEAL 2 study, 50% of women experienced symptomatic response versus 31% of men ($P=.006$). Radiographic regression was also seen in 19% of women versus only 3% of men ($P=.001$). Two groups in Boston have reported that mutations in the adenosine triphosphate (ATP) binding pocket of the endothelial growth factor receptor (EGFR) kinase domain predict for clinical benefit from gefitinib.^{25,26} These findings, if confirmed, may allow for the development of a predictive test for response to this agent.

Erlotinib (Tarceva, OSI) is an agent very similar to gefitinib in terms of structure and activity. It too has been evaluated as a second-line drug in NSCLC with "promising results" in phase II trials. However, unlike gefitinib, a phase III trial has been conducted. The NCIC led a study (JBR-19) comparing gefitinib to supportive care in third-line therapy. This large (>700 patients) study will provide definitive

data regarding response, survival, and quality of life for this group of patients. The manufacturer has revealed that this trial was positive, demonstrating improvements in terms of overall survival, time to progression, and quality of life.²⁷ Full details of this study were presented at the American Society of Clinical Oncology meeting in June 2004.

Other Agents and Ongoing Investigations

Clear recognition that second- and third-line therapies are important is documented by the large number of trials currently planned or in progress. Table 3 lists some of these studies and the agents being evaluated.

Randomized trials with the objective of US Food and Drug Administration registration are currently in progress with TLK286 (Telcyta, Telik). This agent is a rationally designed inhibitor of glutathione-S-transferase P1-1 (GST), which is activated by GST into 2 moieties, one an inhibitor of GST and the other an alkylating agent. The agent also produces apoptosis through a unique stress response mechanism.²⁸

Bexarotene (Targretin, Ligand) is a novel synthetic retinoid analogue. Bexarotene is a subtype-specific ligand, binding preferentially to members of the RXR subclass of receptors (RXR α , RXR β , and RXR γ). Bexarotene differs from all-*trans*-retinoic acid (ATRA), which is a naturally occurring, endogenous hormone that binds with high affinity only to the RAR subtypes, and differs from alitretinoin (Panretin, 9-*cis*-retinoic acid, 9-*cis*-RA), which is a naturally occurring, endogenous "pan-agonist" (ie, binding and activating all known retinoid receptors, including RAR and RXR families). Molecules that are subtype-specific in the binding and activation of retinoid receptors may have unique biological properties that could translate into useful therapeutic agents. Bexarotene has been approved for the treat-

ment of cutaneous T-cell lymphoma. In the course of its development, bexarotene was also evaluated in solid tumors. Phase I trials demonstrated good tolerability and evidence of disease stabilization in NSCLC.²⁹ Recently, a phase I/II trial in NSCLC has demonstrated excellent tolerability and promising survival using targretin in combination with cisplatin and vinorelbine.³⁰ A second trial attempted to evaluate the use of bexarotene as a single agent for consolidation after chemotherapy in stage IV NSCLC in a randomized fashion. While accrual could not be completed, an analysis did demonstrate improved survival for patients treated with bexarotene. Preliminary results of a completed phase II trial at the University of Maryland have demonstrated improved event-free survival when combined with carboplatin/gemcitabine in first-line therapy for NSCLC.³¹ Currently, an industry-sponsored randomized phase II trial is underway evaluating bexarotene as a single agent in third-line therapy (R. Govindan, personal communication, Feb. 2004).

Antitubulin agents have clearly demonstrated activity in NSCLC, with 3 approved in first-line therapy and docetaxel in second-line therapy. Numerous early trials are in progress or have been completed demonstrating activity of new antitubulins or novel preparations of antitubulins in second- and third-line therapy. Cryptophycin, a naturally derived product with activity in resistant cell lines, was inactive in this setting.³² However, BMS-274550, an epothilone B analogue, has demonstrated activity in this setting. Epothilones are naturally derived products that bind at the taxane site on beta-tubulin yet are structurally distinct. Consequently, they are poor substrates for p-glycoprotein and other mechanisms of taxane resistance. In a randomized phase II trial designed to evaluate both activity and tolerability of 2 different schedules, clear activity of BMS-274550 was demonstrated in

Table 3. Current Trials in Second- and Third-Line Therapy of NSCLC

Agent	Class and Mechanism	Eligible Population	Trial Design
ABT-751	Colchicine/ antitubulin	Prior platinum	Phase II
HTI-286	Hemiasterlin/ antitubulin	Prior taxane	Phase II
BMS-275183 ⁴⁵	Taxane/antitubulin	Prior platinum	Phase II
Bexarotene	Retinoid (RXR ligand)	Prior platinum	Randomized phase II vs docetaxel
TLK 286	GST-PI1 inhibitor inhibitor	Prior platinum	Phase III
P2045	Rhenium labeled somatostatin analogue	Previously treated lung cancer	Phase I
Bevacizumab (+ erlotinib)	Anti-VEGF	Prior platinum	Randomized phase II vs docetaxel or pemetrexed
Cetuximab	EGFR inhibitor	Prior platinum	Phase II
Erlotinib	EGFR inhibitor	Prior platinum, docetaxel	Phase III (completed)
Enzastaurin (LY317615) ⁴⁶	PKC-beta antagonist	Prior platinum, taxane (third line)	Phase II
Exisulind (+ docetaxel)	GMP phosphodiesterase inhibitor	Prior platinum	Phase III (completed)
ZD6474 (+ docetaxel) ⁴⁷	VEGF inhibitor	Prior platinum	Phase II
Pivanex (+ docetaxel)	butyrate	Prior platinum	Randomized Phase II vs docetaxel

NSCLC=non-small-cell lung cancer; VEGF=vascular endothelial growth factor; EGFR=endothelial growth factor receptor.

the second-line setting. Of note, responses were seen in patients with prior docetaxel therapy.³³ BMS-184476 is a novel taxane analogue that demonstrated superior activity in xenograft models compared with paclitaxel and docetaxel. It has been evaluated in the second-line setting and appears to be active.³⁴

HTI-286 and ABT-751 are novel antitubulin agents. HTI-286 binds to beta-tubulin at the same site as dolastatin-10. This site overlaps the vinca site.³⁵ ABT-751 binds to the colchicine site on tubulin.³⁶ Both are poor substrates for p-glycoprotein. HTI-286 is currently undergoing evaluation in patients with taxane-resistant disease, while ABT-751 is undergoing evaluation in platinum-treated patients.

Novel platinum agents and modulation of platinum have also been attempted in this setting. ZD0473, a sterically hindered platinum that results in DNA platination resistant to excision by DNA repair systems, was evaluated and found to be inactive.³⁷ Toremifene, an anti-estrogen that at high doses is an antagonist of protein kinase C, was evaluated in combination with cisplatin in platinum-treated NSCLC. The combination was active and tolerable.³⁸ Unfortunately, this strategy has not been evaluated further.

Bevacizumab (Avastin, Genentech) is a monoclonal antibody to the vascular endothelial growth factor (VEGF) receptor. Promising results have been obtained with this agent in combination with standard chemotherapy in first-line therapy of NSCLC.³⁹ In a randomized phase II setting, there appeared to be an increase in time to progression for patients treated with the antibody compared with standard therapy. However, patients with squamous carcinoma had an increased risk of pulmonary hemorrhage. A randomized trial is currently in progress in the frontline setting with adenocarcinoma. In the previously treated population, bevacizumab combined with erlotinib was well tolerated and resulted in an unexpectedly high number of responses.⁴⁰ The Cancer and Leukemia Group B is planning to evaluate this combination in second-line therapy using a randomized phase II design with a control arm allowing physician choice of docetaxel or pemetrexed (M. Socinski, personal communication, Feb. 2003).

Pivanex (pivaloyloxymethylbutyrate) is a novel compound in the butyrate family with differentiating and histone deacetylase inhibitor properties. It was tested in a small phase II trial in patients with 1 or more prior chemotherapy regimens. Half of the patients had received at least 2 prior regimens. The drug demonstrated interesting activity and is now undergoing evaluation in a randomized phase II trial in combination with docetaxel versus single-agent docetaxel.^{41XXXXX}

An interesting avenue of investigation has been to evaluate alternative schedules of currently available agents. Weekly low-dose paclitaxel may have anti-angiogenic effects. Socinski and colleagues⁴² evaluated 62 patients

and obtained an 8% response rate with median survival of 5.2 months and 1-year survival of 20%—results comparable to second-line docetaxel. Building upon these observations, an Italian group added celecoxib to weekly paclitaxel, hypothesizing that this would increase anti-angiogenic activity.⁴³

An intriguing approach to targeted therapy is to perform in vivo imaging of the target prior to administering therapy. This can be done with radiopharmaceuticals in which the targeting moiety can be bound to radioisotopes with either imaging properties (eg, technetium) or therapeutic properties (eg, rhenium). This approach has been successfully employed in therapy of non-Hodgkin lymphoma with ibritumomab (Zevalin, Biogen Idec). Very preliminary data using the somatostatin analogue P2045 (Berlex) indicate that this model may be employed in lung cancer as well.⁴⁴ A phase I trial is currently underway evaluating P2045 in previously treated lung cancer. Several other novel agents are also under investigation (Table 3).

Conclusions

The last decade of the 20th century saw definite progress in the management of advanced NSCLC. Debate has shifted from skepticism regarding the role of any systemic therapy in any group of patients to unquestionable benefit for treatment in both the first- and second-line settings. Despite this progress, the overall benefit remains modest and the outlook for even the healthiest patient with stage IV NSCLC remains dismal. Only the occasional patient will survive 3 years.

While chemotherapy in the first, second, and third lines has demonstrated clear benefit for patients with advanced NSCLC, these treatments remain empiric. A clear goal for the future is more rational selection of agents based upon the actual molecular pathologic characteristics of each patient's tumor rather than solely on clinical criteria. The numerous validated targets (DNA, RNA, tubulin, etc.) of currently available agents and the many new targets under investigation (EGFR, COX-2, VEGF, etc.) should allow for optimal selection of agents. Recent trial designs have been proposed to attempt to take advantage of these features. In addition, more accurate assessments of tumor activity and reassessments of molecular characteristics (circulating tumor cells) with minimally invasive means are likely to be of growing importance in the future.

The goal of transforming advanced NSCLC into a "chronic disease" remains elusive, and a potentially curative treatment is not on the horizon. Nevertheless, significant advances in our understanding of the disease and an increasing ability to define subsets based upon clinical, genomic, and proteomic features coupled with an expanding list of pharmaceuticals with diverse mechanisms of action allow for cautious optimism.

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