Treatment Paradigms for Advanced Stage Non-small Cell Lung Cancer in the Era of Multiple Lines of Therapy

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Abstract: The duration of first-line and the timing of second-line therapy for advanced non-small cell lung cancer has been an area of recent investigation. Five trials have been performed that have investigated shorter (3–4 cycles) versus longer duration of platinum-based therapy; four trials revealed an equivalent overall survival with the shorter duration of therapy, and one trial revealed superior survival with the longer duration of therapy. The toxicity and quality of life data has either been equivalent or favored the shorter duration of therapy. Two trials have investigated the timing of a second-line therapy after completion of four cycles of platinum-based therapy versus the standard treatment paradigm of initiating second-line therapy upon disease progression. Both of these trials have revealed a statistically significant improvement in the progression-free survival, and a trend towards improved survival for the earlier use of second-line therapy. Only 50 to 60% of patients on the standard treatment arm initiated second-line therapy, and the promising results observed are most likely related to the fact that a higher percentage of patients received second-line therapy on the experimental arm. Several trials have investigated maintenance chemotherapy, and these trials have not revealed a survival benefit probably due to the fact that many patients experience disease progression or unacceptable toxicity during the initial or maintenance therapy. The addition of a targeted agent (bevacizumab or cetuximab) to the initial chemotherapy and the continuation of the targeted agent after completion of the chemotherapy have yielded superior overall survival in comparison to chemotherapy alone. The incremental benefit of the maintenance therapy with the targeted agent is unknown.

Key Words: Non-small cell lung cancer, Chemotherapy, Maintenance chemotherapy, Platinum-based chemotherapy.

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Lung cancer is the leading cause of cancer mortality in the United States and it is estimated that in 2008 more patients will die of lung cancer than colon, breast, and prostate cancer combined.[1] Approximately 85% of the cases will be non-small cell lung cancer (NSCLC), and 65% of patients will have advanced stage disease at the time of diagnosis.[2,3] For patients with advanced stage NSCLC and a preserved functional status the standard therapy is double agent platinum-based therapy, although nonplatinum based doublets are acceptable alternative.[4] Most patients who receive first-line chemotherapy will experience disease progression within 3 to 6 months of initiating therapy and the median survival time observed is 8 to 10 months.[5,6] Second-line therapies (erlotinib, pemetrexed, and docetaxel) improve survival and palliate symptoms, but are typically administered at the time of disease progression.[7–10] Erlotinib is approved by the United States Food and Drug Administration (FDA) in the second and third-line setting. The development of effective therapies after initial platinum therapy has raised questions about the duration of first-line therapy, the optimal time to initiate second-line therapy, and the treatment paradigm that is most likely to insure patients receive the three lines of therapy. Recently phase III trials have revealed an improvement in overall survival (OS) with the addition of targeted agents against vascular endothelial growth factor and the epidermal growth factor receptor (EGFR) to platinum-based therapy in comparison to chemotherapy alone.[6,11] In both of these trials the targeted agents were continued after the completion of platinum-based therapy as "maintenance" therapy. It is unclear what the best method of integrating these targeted therapies into our current standard treatment paradigms for second-line therapy. The treatment paradigm that successfully delivers multiple lines of effective therapy or optimizes the therapeutic benefit of all therapies will be the paradigm that is most likely to improve survival.

Several trials have investigated a shorter versus a longer course of platinum based therapy in the first-line settting.[12–16] Recently several trials have investigated the timing of second-line chemotherapy after first-line platinum-based therapy.[17,18] In these trials patients randomized to the experimental arm received treatment with an established second-line agent immediately after the completion of first-line therapy and patients randomized to the standard treatment arm initiated second-line therapy at the time of disease progression.

The variety of treatment strategies investigated in clinical trials, the different agents investigated, and differing

trials designs has created difficulty in determining the optimal treatment strategy.

Further confusing the interpretation of the trials is that a variety of terminology has been used to describe the treatment strategies. This review will use the term duration of therapy to describe trials that investigate a shorter versus longer course of the same platinum-based chemotherapy combination. Trials investigating the treatment strategy of alternating or sequential combinations of therapy are of interest, but are beyond the scope of this review. For purposes of this review the term maintenance chemotherapy will apply to trials that investigated the treatment strategy of initial treatment with a platinum doublet for a set number of cycles and continuation of the nonplatinum agent (i.e., initial therapy with carboplatin and paclitaxel followed by continuation of single agent paclitaxel) or the initiation of a different agent that is currently not approved by the FDA in the second-line setting. Trials that investigate the immediate initiation of a second-line agent approved by the FDA versus observation and initiation of therapy at the time of disease progression are considered trials investigating the timing of second-line therapy. We realize that these distinctions are arbitrary and debatable and they are only intended to provide a structure and clarity for this review.

Another factor making interpretation of these trials difficult is that different primary end-points have been used, and the preferred primary end-point for these trials is a matter of debate. Both progression-free survival (PFS) and OS end-points have advantages and disadvantages. The advantages of the end-point of PFS include earlier assessment of benefit in comparison to OS and the fact that PFS is not confounded by the use of subsequent therapies. Disease progression also often correlates with worsening of patients symptoms and decline in quality of life (QoL). The potential disadvantage of PFS is that a modest difference in PFS may not correlate with improvement in QoL or result in improved OS. The use of OS is perceived as more definitive; however, there can be significant variability in the subsequent therapies available, practice patterns, and therapies such as erlotinib and gefitinib can have significant differences in efficacy depending on the geographic region. Thus, in the current era of multiple lines of therapy the end-point of OS may not be as definitive as in the past. An assessment of QoL may provide additional information to assist in the assessment of the clinical benefit.

Duration of First-Line Platinum Therapy

Several phase III trials have investigated the duration of first-line platinum-based therapy (Table 1). Four of these trials have compared a defined course of therapy (three or four cycles) versus a longer course of therapy (six cycles or until disease progression) and patients were randomized to one of the two treatment arms at the time of enrollment.[12,13,15,16] These trials have revealed equivalent survival, and the QoL has either favored the shorter course therapy[13,16] or been equivalent.[12] The trial by Barata et al., compared four versus six cycles of carboplatin and gemcitabine. The time to tumor progression (TTP) was not significantly different between the four and six cycle treatment arms (4 and 5 months, respectively; $p = 0.077$), but the OS was significantly longer on the six cycle treatment arm in comparison to the four cycle treatment arm ($p = 0.047$). The median survival time on the four and six cycle treatment arms were 7 months (95% confidence interval [CI], 5.9–8.1 months) and 12 months (95% CI, 9.8–14.2 months), respectively but there was no difference in the 1-year survival rate. Approximately 14% of patients on both treatment arms received second-line therapy. The rate of grade 3 or 4 hematologic toxicities and all grades of nausea and vomiting were similar between the two treatment arms.

Park et al.[14] investigated the duration of therapy but used a different trial design; patients received two cycles of cisplatin in combination with a taxane (paclitaxel or docetaxel) or gemcitabine, and then patients who demonstrated stable disease or a response after two cycles were randomized to two or four additional cycles of therapy. The primary end-point of the trial was overall survival, and the trial was designed to demonstrate the noninferiority of four cycles,

TABLE 1. Select Phase III Trials Investigating the Duration of Platinum-Based Therapy

First Author	Year	Chemotherapy	Treatment arms (*n*)	Time to disease progression	Median survival time	1-yr Survival
Smith[13]	2001	MVP	3 cycles (155)	5 mo	6 mo	22%
			6 cycles (153)	5 mo	7 mo	25%
Socinski[12]	2002	CP	4 cycles (114)	NR	6.6 mo	28%
			Continuation (116)[a]	NR	8.5 mo	34%
Von Plessen[16]	2006	CV	3 cycles (150)	16 wk	28 wk	25%
			6 cycles (147)	21 wk	32 wk	25%
Park[14]	2007	Cisplatin-based	4 cycles (156)[b]	4.6 mo[c]	15.9 mo	59%
			6 cycles (158)	6.2 mo	14.9 mo	62.4%
Barata[15]	2007	CG	4 cycles (110)	4 mo	7 mo[c]	NR
			6 cycles (110)	5 mo	12 mo	NR

[a] Patients continued therapy until disease progression or unacceptable toxicity.
[b] Patients who had stable disease or response after cisplatin in combination with paclitaxel, docetaxel or gemcitabine were randomized to two or four additional cycles of therapy. Numbers reflect patients randomized.
[c] *Statistically significant difference in the two treatment arms.*
MVP, mitomycin, vinblastine, cisplatin; CP, carboplatin/paclitaxel; CG, carboplatin/gemcitabine; CV, carboplatin/vinorelbine; NR, not reported.

using a noninferiority margin 15% for a 1-year survival rate with an 80% power. A total of 452 were enrolled, and 314 (69.5%) were randomized. The median number of cycles patients received on the 4 cycle and 6 cycle treatment arms was 4 and 6, respectively. The 1-year survival rates observed on the six-cycle and four-cycle treatment arms were 59% and 62.4%, respectively, and the difference of 3.4% (95% CI −8.0 to 4.8) met the predefined criteria for noninferiority. The TTP on the six and four cycle treatment arms were 6.2 months (95% CI, 5.7–6.7) and 4.6 months (95% CI, 4.4–4.8), respectively ($p = 0.001$). The rates of hematologic and nonhematologic toxicities were similar between the two treatment arms, and there was no evidence of cumulative toxicity. The percentage of patients receiving second-line therapy on the six and four cycle treatment arms were 62.7% and 74.4%, respectively, and the difference was statistically significant ($p = 0.026$). The QoL of the patients on the two treatment arms was similar during the first 4 cycles, but from completion of four cycles to 3 months later patients on the four cycle treatment arm experienced significantly less nausea/vomiting, sore mouth, and dyspnea (<0.05) compared with patients on the six cycle treatment arm. Patients on the four cycle arm also had a significant improvement in role-functioning compared with patients on the six cycle treatment arm.

The data from four of the five trials support a duration of platinum-based therapy for 3 to 4 cycles since longer therapy has not yielded an improvement in OS or QoL. The preliminary results of the trial by Barata et al., support the continuation of therapy to six cycles since there was an improvement in the median survival time and no increased toxicity observed on this trial. The absolute improvement in median survival time (5 months) observed is significant, and is greater than the difference observed with the addition third targeted agent to platinum-based therapy on recent phase III trials.[6,11] The patient characteristics and the rate of second-line therapy are similar, thus it does not appear prognostic factors and subsequent therapies contributed to the difference. The lack of a survival benefit observed on the trial by Park et al., and the statistically significant lower percentage of patients receiving second-line therapy on the six cycle treatment arm is concerning given the fact that second-line therapies have been proven to extend survival and improve QoL. We feel the cumulative data support the use of a shorter duration of first-line therapy.

Maintenance Chemotherapy

Trials investigating maintenance therapy (which for this review has been defined as the continuation of one of the initial agents or the initiation of new agent that is not approved for use in the second-line setting by FDA) have not revealed an improvement in OS (Table 2).[19–21] One significant challenge in assessing this treatment paradigm is that a significant number of patients experience disease progression or unacceptable toxicity during the initial therapy or during the maintenance phase and do not receive the intended therapy. On the trials by Westeel et al.[21] Brodowicz et al.[19] and Belani et al.[20] all patients received platinum-based therapy and only 32, 59%, and 32% of the patients, respectively, underwent randomization to maintenance therapy or observation. In the trial by Westeel et al., only 23% of patients completed the intended course of weekly vinorelbine for 6 months, and in the trial by Belani et al., only 23% of patients completed the four full cycles of weekly paclitaxel.

In the trial by Brodowicz et al.[19] patients received initial therapy with cisplatin and gemcitabine, and were randomized to single agent gemcitabine or observation, and the median number of cycles of single agent gemcitabine (days 1 and 8 every 21 days) was 3 (range 0–38). The primary end-point was TTP throughout the whole study period. The time tumor progression observed on the gemcitabine and observation arms throughout the study period was 6.6 and 5 months ($p < 0.001$), respectively; the TTP after randomization was 3.6 and 2.0, respectively ($p < 0.001$). The median OS times observed on the gemcitabine and observations arms throughout the study period were 13.0 and 11.0 months, respectively ($p = 0.195$), and after randomization were 10.2 and 8.1, respectively ($p = 0.172$). The trial by Belani et al., was not statistically powered to assess the efficacy of the maintenance paclitaxel. The median TTP on the paclitaxel and observation arms were 38 and 29 weeks, respectively; and the median survival time was 75 weeks and 60 weeks, respectively. On the Westeel et al., trial the median progression free survival times observed on the vinorelbine and observation arms were 5 and 3 months (hazard ratio [HR] = 0.77; 95% CI, 0.56–1.07, $p = 0.11$), and the median OS times observed on both arms was 12.3 months (HR = 1.08; 95% CI, 0.79–1.47, $p = 0.65$).

TABLE 2. Select Phase III Trials of Maintenance Chemotherapy

First Author	Year	Chemotherapy (n)[a]	Median Progression-Free Survival	Median Overall Survival Time
Westeel[21]	2005	Vinorelbine (91)	5 mo[b]	12.3 mo[b]
		Observation (90)	3 mo	12.3 mo
Belani[20]	2003	Paclitaxel (65)	38 wk	75 wk
		Observation (65)	29 wk	60 wk
Brodowicz[19]	2006	Gemcitabine (138)	3.6[c] mo	10.2 mo
		Observation (68)	2.0 mo	8.1 mo

[a] N-values represent number of patients randomized.
[b] The hazard ratio of progression-free survival was 0.77 (95% CI, 0.56–1.07; $p = 0.65$), and the hazard ratio for overall survival was 1.08 (95% CI, 0.79–1.47; $p = 0.65$).
[c] Data reported as time after randomization and for time to tumor progression p value <0.001, and for overall survival p value = 0.172.

This data has raised questions about the feasibility and benefits of this approach, and it has not been widely implemented. However, the difference in TTP observed and a trend towards an improvement in OS did initiate an interest in developing other trials with other agents and trial designs where patients were randomized to further therapy or observation after completion of the initial therapy.

Timing of Second-Line Therapy

The current standard treatment paradigm is to treat patients for a defined number of cycles of first-line chemotherapy and observe the patient for symptomatic or radiographic evidence of disease progression.[4] At the time of disease progression patients in the United States are generally initiated on second-line therapy with one of the three agents (doectaxel, pemetrexed, and erlotinib), and in some countries gefitinib is available. The standard method of monitoring for disease progression has not been established, and undoubtedly there is variability in the frequency of clinic visits and radiologic testing of patients. The rate of patients receiving second-line therapy on recent phase III first-line trials is 50 to 60%.[6,11,22] Recently there have been two phase III trials that have investigated the timing of initiating second-line therapy. On both of these trials patients received four cycles of initial platinum-based therapy and were randomized to the standard treatment paradigm or the experimental paradigm of initiating second-line therapy immediately after completion of platinum-based therapy.

On the trial by Fidias et al.[17] patients received four cycles of carboplatin and gemcitabine and patients experiencing a response or stable disease were randomized to immediate docetaxel versus the initiation of docetaxel at the time of disease progression (Table 3). On both treatment arms patients received docetaxel until disease progression, unacceptable toxicity, or a maximum of six cycles. Patients on the immediate docetaxel arm were seen every 3 weeks and underwent scans after every two cycles (6 weeks), and then after completion of six cycles therapy had follow-up visits every 3 weeks. Patients on the standard arm were seen by a physician every 3 weeks and underwent repeat imaging every 3 months or if clinically indicated by the treating physician. The primary end-point was OS from the date of randomization, and preliminary results are available. A total of 552 patients were enrolled, 307 patients experienced stable disease or a response; 153 patients were randomized to immediate docetaxel and 142 (93%) received treatment, and 154 patients were randomized to delayed docetaxel and 91 (59%) received treatment. The median OS of the randomized population on the immediate and delayed docetaxel arms were not significantly different (11.9 and 9.1 months, respectively, $p = 0.071$). The median PFS of the randomized patient population on the immediate and delayed docetaxel arms was significantly longer than the delayed arm ($p = < 0.0001$). There was no significant difference in the QoL between the two treatment arms. Of the patients on the delayed docetaxel arm who did not receive therapy ($n = 63$) the main reasons on preliminary review were: disease progression ($n = 25$), unknown or missing ($n = 12$), patient decision ($n = 10$), death ($n = 4$), investigator decision to change therapy ($n = 3$), and withdrew consent ($n = 2$).

The preliminary data from the trial by Fidias et al.[17] reveals a promising trend towards an improvement in OS, and a particular strength of this trial is that the second-line therapy was the same in both treatment arms. Thus, this trial design eliminates variability in the type of agents used in the second-line therapy, and the use of agents that are not approved by the FDA in the second-line setting. One interesting comparison will be the OS of patients who received docetaxel on the immediate docetaxel arm and on the delayed docetaxel arm. If the OS is similar for patients receiving docetaxel on both treatment arms it would be suggestive that the difference in OS observed on the randomized population was related to a difference in the rate of delivery of second-line therapy.

A trial by Ciuleanu et al.[18] randomized patients after four cycles of a platinum-doublet to either pemetrexed or placebo every 3 weeks.[18] Patients on both arms were seen by a physician every cycle, and underwent radiologic imaging every two cycles (6 weeks). On the placebo arm the choice of second-line therapy upon disease progression was at the discretion of the physician, and 11% of patients received pemetrexed as second-line therapy. The primary end-point was PFS from the time of randomization. The median number of cycles of therapy on the pemetrexed and placebo arms were 4 (range 1–34) and 3 (range 1–30), respectively. This trial revealed a statistically significant improvement in the PFS with the immediate initiation of pemetrexed, and preliminary OS results revealed a statistically nonsignificant difference in OS with 55% of the patients censored (Table 3). When subsequent therapies were analyzed 37.2% of patients on the pemetrexed and 50% of patients on the placebo arm received subsequent systemic therapies ($p = 0.008$). The types of subsequent therapies patients received were balanced between the two treatment arms.

In a subset analysis there was a statistically significant difference in OS in patients with nonsquamous histology ($n = 482$). A median survival of 14.4 months was observed in patients nonsquamous histology who initiated immediate pemetrexed in comparison to 9.4 months for patients who were on the observation arm ($p = 0.005$). The PFS for patients who immediately received pemetrexed and on the observation arm were 4.37 and 1.84 months, respectively ($p < 0.00001$). In the patients with squamous histology ($n = 181$) a median survival of 9.6 months was observed in patients who immediately initiated pemetrexed in comparison to 11.9 months for patients on the observation arm ($p = 0.231$) The PFS on the immediate pemetrexed and observation arms were 2.43 and 2.50, respectively ($p = 0.896$). Retrospective data from a phase III second-line trial comparing docetaxel verses pemetrexed, and a prospective subset analysis of cisplatin/pemetrexed versus cisplatin/gemcitabine in the first-line setting have demonstrated a similar interaction between histology and efficacy of pemetrexed.[22,23] The cumulative data from these analyses indicates that the efficacy of pemetrexed in patients with squamous histology is limited, and pemetrexed should only be used in patients with nonsquamous histology.

TABLE 3. Select Trials of Immediate Second-line vs Delayed Second-Line Therapy

First Author	Year	No. of Patients Randomized	No. of Patients Treated	Treatment	Median PFS (95% CI) (mo)	*p*	OS Median (95% CI) (mo)	*p*
Fidias[17]	2007	307	142	Immediate	6.5 (4.4–7.2)	<0.0001	11.9 (10–13.7)	0.071
			91	Delayed	2.8 (2.6–3.4)		9.1 (8.0–11.2)	
Cinleanu[18]	2008	663	432	Pemetrexed	4.04 (3.06–4.44)[a]	<0.00001	13.01 (11.40–14.42)	0.060[a]
			221	Placebo	1.97 (1.54–2.76)		10.18 (8.57–13.17)	
Nonsquamous		482	NR	Pemetrexed	4.37	<0.00001	14.4	0.005
Subset			NR	Placebo	1.84		9.4	
Squamous		181	NR	Pemetrexed	2.43	0.896	9.6	0.231
Subset			NR	Placebo	2.50		11.9	

[a] Progression-Free Survival hazard ratio (HR) = 0.599 (95% CI: 0.49–0.73); *p* value <0.0001; Overall Survival HR = 0.798 (95% CI: 0.63–1.01) *p* value = 0.060.
PFS, Progression-free survival; OS, overall survival; NR, not reported; CI, confidence interval.

These two trials reveal a flaw with the current treatment paradigm of monitoring patients and initiating therapy at the time for disease progression. With this approach 40 to 50% of patients on the trials by Fidias et al., and Ciuleanu et al., never initiated second-line therapy. The rate of patients not receiving second-line therapy is similar to the rate observed on recent phase III first-line trials of first-line therapy.[6,11,22] There are multiple reasons for the rate of second-line chemotherapy delivery observed on these trials. Many patients may not be appropriate candidates for second-line therapy due to decline in performance status, intercurrent illnesses, and some patients may elected not to initiate second-line therapy. However, a certain percentage of patients experience rapid disease progression after completion of first-line therapy and are consequently not candidates for second-line therapy. This patient population may benefit from the immediate initiation of second-line therapy provided they are able to tolerate and experience stable disease or a response to the therapy. There is also a patient population that will experience a durable response or stable disease after first-line therapy, and this patient population may not benefit from the immediate initiation of second-line therapy. Thus, the heterogeneity and unpredictability of NSCLC make it difficult to anticipate the optimal time to initiate and to select the patient population who will benefit from the immediate initiation of second-line therapy.

On both of these trials the patients were seen by a physician every 3 weeks and assessed for symptomatic progression, and the interval of radiologic assessment for disease progression was every 6 weeks on both arms on the trial by Ciuleanu et al., or every twelve weeks on the delayed docetaxel arm on the trial by Fidias et al., The median progression-free period after randomization on the placebo arms observed on the trials by Fidias et al., and Ciuleanu et al., were 2.8 and 1.97 months, respectively. Thus, on the both trials a significant percentage of patients had symptomatic progression soon after completion of the initial platinum therapy, and even with the every 6 week imaging on the trial by Ciuleanu only 50% of patients on the placebo arm received second-line therapy. Thus, it does not appear more frequent clinic visits or radiologic imaging will be sufficient to detect progression before it adversely impacts the patients' ability to receive second-line therapy.

The proper selection of patients will be critical to the future development of this treatment paradigm, and even under the best of circumstances not all patients will be candidates or benefit from the early initiation of second-line therapy. Patients with a good baseline performance status, female gender, and nonsquamous histology are more likely to receive second-line therapy.[24] In previous analyses of second-line therapy the best response to first-line therapy, performance status, gender, and stage at diagnosis have been found to prognostic.[25,26] The time since completion or time from initiation of first-line chemotherapy has been found to be prognostic as well.[10,25] A combination of clinical and molecular factors yet to be clearly defined may allow the selection of the patients most-likely to benefit from the immediate initiation of second-line therapy. The use of pemetrexed with this strategy should be restricted to patients with nonsquamous histology.

Meta-Analysis

To evaluate the effect of duration of chemotherapy recently a meta-analysis[27] was performed on this subject which included 13 trials[12–17,19–21,28–31]The meta-analysis performed for the end-point PFS ($n = 1907$) revealed an improvement in PFS with extending chemotherapy duration, and if a subset analysis was performed the improvement in PFS was statistically significant with third generation therapies ($n = 1524$) but not with therapies that did not contain a third generation agent ($n = 382$). When the meta-analysis is performed for the end-point of OS ($n = 2416$) the extension of chemotherapy did not have an effect on OS, and there was no improvement in OS with third generation agents. The lack of improvement in OS was still present with the meta-analysis was performed using the 10 best quality trials ($n = 2267$). If the meta-analysis is repeated for the end-point of OS including the preliminary survival results from the trial by Ciuleanu et al., ($n = 3079$) then the meta-analysis does reveal an improvement in OS (HR = 0.92, 95% CI 0.86–0.99; $p = 0.03$). In our opinion, this meta-analysis does not support extending the duration of therapy at this time since the

TABLE 4. Results of West Japan Thoracic Oncology Trial (WJTOG 0203)

First Author	Year	Treatment (*n*)	Median PFS (mo)	HR	Median OS (mo)	HR
Hida[32]	2008	Chemotherapy alone (298)	4.27	0.68 (95% CI 0.57–0.80) p value<0.001	12.89	0.86 (96% CI 0.72–1.03) $p = 0.10$
		Chemotherapy→ Gefitinib (300)	4.60		13.68	
Overall survival						

Subset analysis	Treatment	Median OS	*p*
Adenocarcinoma ($n = 467$)	Chemotherapy alone	14.33	$p = 0.03$
	Chemotherapy→ Gefitinib	15.42	
Nonadenocarcinoma ($n = 128$)	Chemotherapy alone	9.17	$p = 0.24$
	Chemotherapy→ Gefitinib	7.69	
Never-smoker ($n = 185$)	Chemotherapy alone	23.51	$p = 0.72$
	Chemotherapy→ Gefitinib	21.65	
Smoker ($n = 410$)	Chemotherapy alone	10.03	$p = 0.03$
	Chemotherapy→ Gefitinib	11.67	

PFS, progression-free survival; HR, hazard ratio; OS, overall survival; NR, not reported; CI, confidence interval.

survival results from the trial by Ciuleanu et al., are not mature. It also may not take into account the differential effect that effective second-line therapies have on survival.

Gefitinib

A trial by the West Japan Thoracic Oncology Group investigated the role of gefitinib after platinum-based therapy (Table 4).[32] Patients enrolled on this trial were randomized to ≥3 cycles of platinum-based therapy or three cycles of platinum-based therapy followed gefitinib, and the primary end-point was OS. The median number of chemotherapy cycles on both arms was three, and on the chemotherapy followed by gefitinib 172 (57%) patients initiated gefitinib. On poststudy therapy approximately 35% of patients received docetaxel on both arms, and on the chemotherapy alone arm 51.3% received gefitinib and on the chemotherapy followed by gefitinib arm 28.6% continued to receive gefitinib. There was a significant improvement in PFS, but no significant difference in OS (Table 4). On a subset analysis of patients with adenocarcinoma histology ($n = 467$) a significant improvement in OS with chemotherapy followed by gefitinib was observed. When a subset analysis was performed on smoking status the patients with a history of never smoking ($n = 185$) had a similar survival with both treatments, but 76% of patients assigned to the chemotherapy alone arm subsequently received gefitinib. This trial included a large number of patients with a higher prevalence of activating epidermal growth factor mutations (EGFR) (31% of patients were never smokers, 100% were Asian, 78% had adenocarcinoma histology) and the applicability of this treatment paradigm in patient populations with a lower rate of activating EGFR mutations is yet to be determined. The fact that patients on both treatment arms received a median of three cycles of chemotherapy and 50% of the patients on chemotherapy alone subsequently received gefitinib makes interpretation of the initial therapy's impact on survival challenging.

Maintenance Therapy with Targeted Agents

Two phase III trials that have investigated platinum-based therapy with or without bevacizumab or cetuximab have revealed an improvement in OS.[6,11] A second phase III trial with bevacizumab revealed an improvement in PFS but not in OS[33] and a second phase III trial with cetuximab did not reveal an improvement in PFS or OS.[34] All four of these trials continued the targeted agent after completion of the combination of chemotherapy and the targeted therapy. The hypothesis is that the continuation of the targeted agent would delay disease progression and improve overall survival, and the treatment with the targeted agent alone would be well tolerated. Eastern Cooperative Oncology Group trial 4599 revealed an improvement in OS with the addition of bevacizumab to carboplatin and paclitaxel.[6] Of the 407 patients who received carboplatin, paclitaxel and bevacizumab 215 (53%) received bevacizumab monotherapy and of these 107 (50%) received greater than five cycles of therapy. On the phase III trial of cisplatin and vinorelbine with and without cetuximab (the FLEX trial) 241 of 548 patients did not experience progressive disease or unacceptable toxicity and were eligible for maintenance therapy, and 80% of the eligible patients received cetuximab.[11] The median duration of therapy was 18 weeks. The data from these trials indicate this approach is feasible, but they do not provide data about the incremental benefit of continuing the targeted agent beyond completion of the initial treatment with combination of the targeted agent and chemotherapy. The single agent activity of bevacizumab and cetuximab in NSCLC appears to be modest,[35,36] and concerns about acute and potential cumulative toxicities as well as the economic costs have raised questions about this practice. To accurately assess the risks and benefits of maintenance therapy with bevacizumab or cetuximab a well designed phase III trial investigating this clinical question would be required. Currently our practice when

incorporating bevacizumab into the first-line therapy has been to continue the bevacizumab until disease progression or unacceptable toxicity based on the treatment paradigm used in ECOG 4599. If cetuximab receives approval by the FDA for NSCLC we will continue single agent cetuximab after completion of chemotherapy based on the treatment paradigm used in the FLEX trial.

CONCLUSIONS

We believe the standard initial duration of platinum-based therapy should be three to four cycles since four of the five trial investigating the duration of platinum therapy in the first-line setting have revealed equivalent survival with the shorter duration of therapy.[37] The immediate initiation of agents with proven activity in the second-line after completion of four cycles platinum-based therapy appears to be the most promising treatment strategy due to the fact that a higher percentage of patients received second-line therapy in comparison to our current treatment paradigm. These two trials also illustrate that the proper selection of the end-point for trials is problematic and has yet to be determined. For instance, the trial by Fidias et al., employed the primary end-point of OS and is considered a "negative" trial while the trial by Ciuleanu et al., used the primary end-point of PFS and is considered a "positive" trial despite a similar absolute improvement in PFS and OS observed in the two trials. Even if the paradigm of immediate initiation of second-line agents is implemented a significant percentage of patients will not be candidates for further treatment and will not benefit from this treatment paradigm. The proper selection of patients will most likely depend on clinical factors including histology and smoking history, molecular factors such as the presence or absence of activating EGFR mutations, the toxicity the patients experienced during the initial therapy, and physician and patient preferences. Inevitably clinicians will be required to make an individual assessment of the data and whether it applies to an individual patient and discuss the potential advantages and disadvantages of a treatment strategy with the patient.

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