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.