Maintenance Therapy and Advanced Non–Small-Cell Lung Cancer

A Skeptic's View

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Abstract: Maintenance chemotherapy has a long history of use in hematologic malignancies, in which the benefits are considerable in terms of survival and quality of life. Recently, several studies have demonstrated that maintenance therapy in non–small-cell lung cancer can prolong overall survival in patients who have benefited from initial platinum-based chemotherapy. These studies have led to regulatory approval of two agents (pemetrexed and erlotinib) in this setting. We raise several issues regarding the design and execution of these studies, which question the validity of these conclusions, and explore aspects of the trial results concerning the optimal use of this approach, if it is to be accepted.

Key Words: Non–small-cell lung cancer, Chemotherapy, Duration, Maintenance.

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Maintenance therapies are generally used for chronic malignant diseases, that is, those diseases that may be controlled for years with long-term treatments. Maintenance treatment with low-dose chemotherapeutic agents to prevent disease recurrence once remission has been achieved is a classical approach (and terminology) used in various hematologic malignancies. Recently, an extensive body of research has emerged concerning maintenance therapy in advanced non–small-cell lung cancer (NSCLC). In contrast to the situation in hematologic malignancy, the potential survival benefit is much more limited. Numerous reviews have been published in the past several years regarding this topic.[1–5] Many of these articles include a variety of studies done over the past two decades. In fact, only a few recent studies using modern agents are truly relevant to the question. These trials break down into two approaches regarding maintenance (Table 1). First, the trials that transition from a standard platinum doublet to a different single agent (switch maintenance). Such trials are, in fact, about the optimal timing for introducing second-line therapy. Second, the trials that continue to administer the nonplatinum agent (continuation maintenance). Such trials are about the optimal duration of frontline therapy. Five randomized trials have been reported that employ the switch-maintenance strategy, each with a different agent.[6–11] The investigators logically chose agents that have demonstrated activity in patients who have progressed after prior platinum-containing therapy.[12–14] Three other trials have evaluated continuation maintenance.[15–18] One of those studies evaluated both strategies.[16] Our article will not address the case of bevacizumab continuation in NSCLC because this strategy has not been evaluated in a randomized setting.

There seems little doubt that continuation of chemotherapy (either by changing to a new agent or by continuing with the nonplatinum portion of the initial regimen) will prolong progression-free survival (PFS) (Table 1). We believe that it is more important to determine whether this approach actually prolongs overall survival (OS) and/or the quality of life at an acceptable cost for patients and for society and is not an artifact of trial design or interpretation. We raise the following questions regarding these studies:

Is There a Fundamental Advantage for the Early Introduction of Additional Agents?

The initial impetus for the use of maintenance therapy was based upon mathematical and preclinical models indicating that the early introduction of additional agents would be of benefit.[19,20] The basic theory is that the use of these agents at a time of lower tumor burden would be beneficial because there would be fewer clones of inherently resistant cells. If this hypothesis is correct, then there should be a survival advantage of the experimental (i.e., maintenance or early introduction) arm over the patients on the control (i.e., late introduction) arm that actually received the "study drug." However, the weight of evidence is that this hypothesis has not been proved by these studies. The Fidias[6] trial specifically reported the outcomes of control patients who received docetaxel and showed no difference.

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TABLE 1. Trials of Maintenance Chemotherapy

	Study	Agent	PFS (mo)	OS (mo)
Switch maintenance	Fidias6	Docetaxel	5.7*	12.3
		Control	2.7	9.7
	JMEN	Pemetrexed	4.3*	13.4
		Control	2.6	10.6
	SATURN	Erlotonib	2.8*	12.0*
		Control	2.6	11.0
	ATLAS	Erltonib	4.8*	15.9
		Control	3.8	13.9
	INFORM	Gefitinib	4.8*	18.7
		Control	2.6	16.9
Continuation maintenance	Belani[15]	Gemcitabine	7.4	8.0
		Control	7.7	9.3
	IFCT-GFPC 0502	Gemcitabine	3.8 *	12.1
		Erlotinib	2.9*	11.4
		Control	1.9	10.8
	PARAMOUNT	Pemetrexed	3.9*	13.86*
		Control	2.6	11.1

*$p < 0.05$; PFS, progression-free survival; OS, overall survival; ATLAS, Phase IIIb, multicenter, randomized, placebo-controlled trial to evaluate the safety and efficacy of chemotherapy+bevacizumab followed by bevacizumab+erlotinib versus bevacizumab+erlotinib placebo in subjects with locally advanced or metastatic NSCLC; INFORM, Iressa in Non-small cell for Maintenance; SATURN, Sequential Tarceva in Unresectable NSCLC; IFCT-GFPC, Intergroupe Français de Cancérologie Thoracique-Groupe Français de Pneumo-Cancérologie; PARAMOUNT, Phase III Study of Maintenance Pemetrexed (Pem) Plus Best Supportive Care (BSC) Versus Placebo Plus BSC Immediately Following Induction Treatment with Pem Plus Cisplatin for Advanced Nonsquamous Non-small Cell Lung Cancer.

TABLE 2. Control Arm Therapy at Progression

Study	Agent	Crossover (%)	Any Agent (%)
Fidias[6]	Docetaxel	62	62
JMEN	Pemetrexed	18	67
SATURN	Erlotonib	21	72
ATLAS	Erlotinib	40	56
Belani[15]	Gemcitabine	N/A*	17
IFCT-GFPC 0502	Gemcitabine Erlotinib	N/A*	91
PARAMOUNT	Pemetrexed	N/A*	64
INFORM	Gefitinib	30 (includes erlotinib)	67

*N/A not applicable, study of continuation maintenance, all patients received drug as part of induction.

ATLAS, Phase IIIb, multicenter, randomized, placebo-controlled trial to evaluate the safety and efficacy of chemotherapy+bevacizumab followed by bevacizumab+erlotinib versus bevacizumab+erlotinib placebo in subjects with locally advanced or metastatic NSCLC; INFORM, Iressa in Non-small cell for Maintenance; SATURN, Sequential Tarceva in Unresectable NSCLC; IFCT-GFPC, Intergroupe Français de Cancérologie Thoracique-Groupe Français de Pneumo-Cancérologie; PARAMOUNT, Phase III Study of Maintenance Pemetrexed (Pem) Plus Best Supportive Care (BSC) Versus Placebo Plus BSC Immediately Following Induction Treatment with Pem Plus Cisplatin for Advanced Nonsquamous Non-small Cell Lung Cancer.

TABLE 3. Benefits of Maintenance and Response Status

Study	Agent	Responder HR	Stable Disease HR
Fidias[6]	Docetaxel	0.61* (OS)	1.02 (OS)
JMEN	Pemetrexed	0.81 (OS)	0.61†(OS)
SATURN	Erlotonib	0.94 (OS)	0.72† (OS)
ATLAS	Erlotinib	NR	NR
Belani[15]	Gemcitabine	NR	NR
IFCT-GFPC 0502	Gemcitabine	NR	NR
PARAMOUNT	Pemetrexed	0.48† (PFS)	0.74 (PFS)
INFORM	Gefitinib	NR	NR

**p* value not reported.

†$p < 0.05$.[2]

OS, overall survival; PFS, progression-free survival; NR, not reported; HR, hazard ratio; ATLAS, Phase IIIb, multicenter, randomized, placebo-controlled trial to evaluate the safety and efficacy of chemotherapy+bevacizumab followed by bevacizumab+erlotinib versus bevacizumab+erlotinib placebo in subjects with locally advanced or metastatic NSCLC; INFORM, Iressa in Non-small cell for Maintenance; SATURN, Sequential Tarceva in Unresectable NSCLC; IFCT-GFPC, Intergroupe Français de Cancérologie Thoracique-Groupe Français de Pneumo-Cancérologie; PARAMOUNT, Phase III Study of Maintenance Pemetrexed (Pem) Plus Best Supportive Care (BSC) Versus Placebo Plus BSC Immediately Following Induction Treatment with Pem Plus Cisplatin for Advanced Nonsquamous Non-small Cell Lung Cancer.

Interestingly, no other study has reported the outcomes for control patients who either crossed-over to the "study agent" or to another acceptable drug. Unlike the situation with truly experimental drugs where there are questions regarding the benefits of a drug, most of the agents employed in these trials have been demonstrated to be active in patients who have progressed after treatment with platinum-based chemotherapy in prior randomized phase III trials, that is, pemetrexed and erlotinib. The exception is gemcitabine, which has demonstrated second-line activity in a multicenter phase II trial.[21]

Did the Control Group Perform Adequately?

This is perhaps the most significant and important issue with these trials. There are at least two major issues. First, did patients receive appropriate treatment upon disease progression? This is very questionable. To begin with, an unacceptably high number of patients failed to receive any therapy (Table 2). Depending upon the trial, this is up to 60% of patients. Proponents of maintenance will point to data that indicate that this is consistent with the overall use of second-line therapy. However, those figures apply to the overall lung cancer population, *not* to those who would have been randomized on this trial. It must be recalled that the requirement for randomization was that patients were stable or responding after four courses of platinum-based chemotherapy, had a PS 0 to 1, and had normal organ function. It is clear that where second-line therapy is mandated (e.g., the Intergroupe Français de Cancérologie Thoracique-Groupe Français de Pneumo-Cancérologie [IFCT-GFPC] study), at least 80% of the patients received second-line treatment. Furthermore, on the JMEN (pemetrexed maintenance) study, less than 20% of the patients received pemetrexed at the time of progression and only 50% received an appropriate agent (i.e., pemetrexed, docetaxel, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor [TKI] or research study) as second-line therapy. Similarly, in the Sequential Tarceva in Unresectable NSCLC (SATURN) trial, although 72% of the patients received some sort of second-line therapy, only 21% of the patients received erlotinib. The other agents are reported only in broad classifications (e.g., *antimetabolite* or *taxane*) rather than as the specific agents. In an era in which second-line treatment

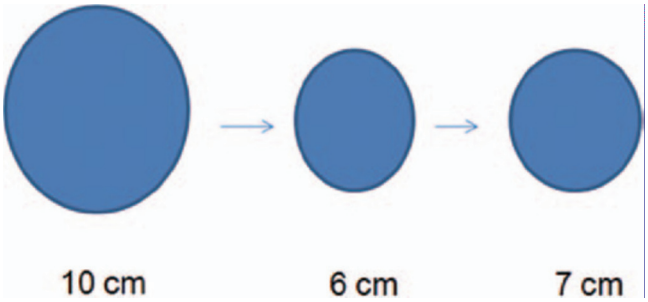

FIGURE 1. "Stable" disease is sometimes early progression.

has been clearly established, and established with specific drugs, it is simply not acceptable for studies that ask a question of early versus delayed therapy to fail to assure that patients are appropriately treated. In short, patients on the control arms received substandard care and therefore, the results are questionable.

If This Approach is Valid, Who Actually Benefits?

As one evaluates the data from these trials in greater depth, certain other patterns emerge. Most importantly, who actually benefits from maintenance? The SATURN (i.e., erlotinib) study provides the clearest information. The population that benefitted was patients with *stable disease*, with absolutely no benefit seen for those with actual responses. The European Medicines Agency felt that the indication for erlotinib in this setting should be restricted to patients with stable disease and not for those with response.[22] Why is this important? It points to a fundamental problem with the definition of stable disease. Such patients can in fact have up to a 20% increase in the size of tumors and therefore in reality have disease progression, though not meeting the formal definition.[23] As demonstrated in Fig. 1, many stable patients may, in fact, be patients with early progression. Over the past few years, Waterfall plots have become a popular method of illustrating data as these graphs much more clearly indicate the actual status of patient response as opposed to the binary approach of response/stable versus progressive disease. A reasonable hypothesis is that the benefit seen from maintenance in fact represents the early introduction of second-line therapy in a slowly progressing population of patients. This point is also fundamental when one contemplates the issue of why patients on the control arm were not treated. We will return to this issue shortly.

Another question, specifically relevant to the use of the EGFR TKIs, is whether patients who are EGFR wild-type (wt) benefit. The two trials that have been reported with muational data (Iressa in Non-small cell for Maintenance [INFORM] and SATURN) clearly show marked PFS differences for the TKI n patients with activating mutations (hazard ratio [HR] = 0.10 and median PFS of 16.6 months [versus 2.8 months] for INFORM and HR = 0.10 reported for SATURN). The third trial Phase IIIb, multicenter, randomized, placebo-controlled trial to evaluate the safety and efficacy of chemotherapy+bevacizumab followed by bevacizumab+erlotinib versus bevacizumab+erlotinib placebo in subjects with locally advanced or metastatic NSCLC (ATLAS) has not been completely reported. Although there is a statistically significant benefit for *wt* patients, it is much less marked than that seen for mutated patients. In the INFORM trial, the HR is 0.86 with a median PFS of 2.7 months versus 1.5 months (control) for wt patients; clearly, any benefit is minimal. The survival curves are essentially identical. In the SATURN study, the HR is 0.78 and the median PFS or OS are not reported (visual inspection of the published curves reveals very modest differences). Furthermore, the OS results are not reported and because of the crossover effect, they are likely to be minimal. In summary, there is, at best, a slight advantage to maintenance EGFR TKIs in the EGFR wt population.

Why did Control Patients not Receive Second-Line Therapy?

Related to the issue that patients who benefit from second line are those who are progressing but have not yet met the official definition of PD, is the timing of the introduction of therapy for those on the control arm. In most practices, an off-study patient would receive second-line treatment at the first indication of clinical or radiological progression. This might very well mean at a time when there is a 10% to 15% increase in tumor size as opposed to the Response Evaluation Criteria in Solid Tumours (RECIST) defined 20% increase or when there is a clinical but nonmeasurable progression. To the extent that patients do not receive treatment because "they fell off the cliff", i.e. progressed to such an extent that declining performance status, disease complications or death occurred suddenly, it may very well be a result of study design overcoming normal decision making. We have not been provided with any data regarding why patients on the control arm did not receive additional therapy. This issue is critical. The question of maintenance (and particularly the switch maintenance approach) is not one of treatment versus no treatment. Rather, it is a question of early versus late introduction of proven agents. Once again, the failure to assure that patients on the control arm received (or even had access to) the *experimental agent* is a serious design flaw.

Are Four Cycles of Platinum-Based Chemotherapy Truly Adequate?

All the maintenance trials have randomized patients after four courses of platinum-based therapy. This approach has been based upon a number of studies that indicated that most, if not all, benefit from initial chemotherapy occurred during the first four courses.[24–26] These studies and analyses led to recommendations that patients with advanced NSCLC should be treated with four to six courses of platinum-based chemotherapy.[27] However, it is still quite common in practice and part of several guidelines (American Society of Clinical Oncology, National Comprehensive Cancer Network) to employ six cycles of therapy, and further tumor shrinkage is frequently observed between the fourth and the sixth cycle of chemotherapy.[28,29] There is no evidence to date that the use

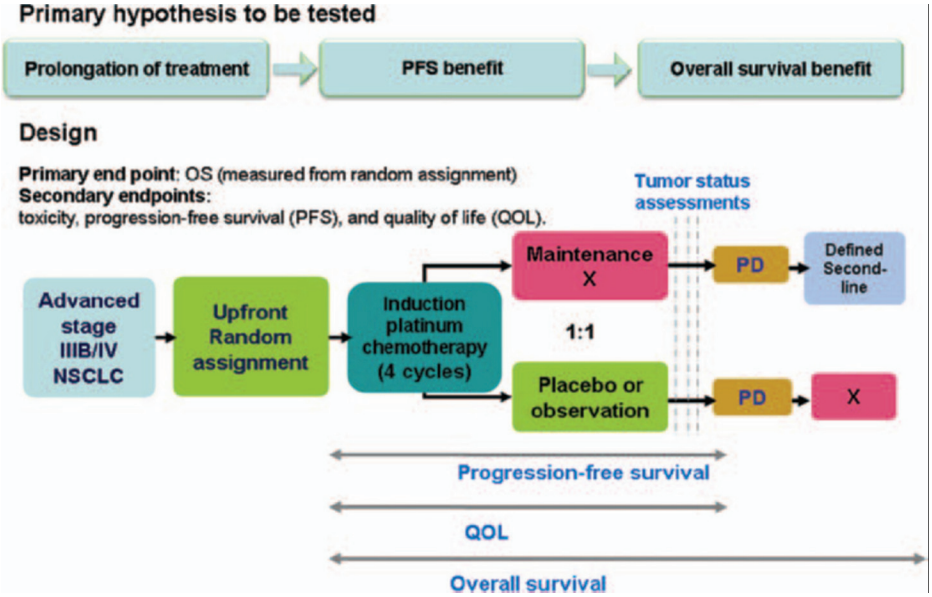

FIGURE 2. Optimal design of a switch-maintenance trial. NSCLC, non–small-cell lung cancer; OS, overall survival; PD, progressive disease.

of maintenance after six courses of therapy is advantageous although the population able to tolerate six cycles is probably the population able to tolerate maintenance therapy. In other terms, the PFS benefit seen with maintenance trials in patients who have received four cycles of platinum-based therapy may be very similar and likely identical to the one obtained when continuing first-line doublets to six cycles.

Furthermore, one of the pivotal trials that form the basis of this recommendation for four cycles of chemotherapy is probably no longer relevant to this discussion. Socinski[25] compared four cycles of carboplatin/paclitaxel with an indefinite number of cycles. The major limiting factor was cumulative neurotoxicity (19% at 4 cycles, 43% at 8 cycles) due to paclitaxel. There was no difference in OS in this relatively small study (n = 230) though there was a numerical advantage for longer therapy (8.5 months versus 6.6 months, p = 0.63). In current practice, the use of pemetrexed-based regimens has supplanted taxane-based therapy for nonsquamous cancers. For squamous disease, gemcitabine-containing regimens offer comparable efficacy without the risk of neurotoxicity.

Which Study Might Answer the Question of Maintenance?

In fact, the real question in clinical practice is the strategy of first-line chemotherapy for patients with advanced NSCLC and a good PS: Is it more appropriate to treat patients *minimally*, that is, with four to six cycles of a platinum doublet and offer a treatment holiday with close observation and rapid initiation of second-line therapy at the time of radiologic or symptom progression? Such a holiday offers freedom from treatment-related toxicity, inconvenience, and expense. Or is it better to treat them maximally, taking into account the tolerance of the treatment, clinical and radiological response, and the patient's preference? This approach has almost invariably been associated with a PFS benefit. For patients receiving switch maintenance it assures exposure to the second-line treatment.

To answer these questions, we need appropriately designed studies to properly assess these strategies and to determine whether there are specific populations of patients who might benefit. There must be a clear assessment of both the risks (including financial risk) and benefits. Randomization should be performed before any therapy is started, and an evaluation of quality of life should be mandatory. All patients in the short-treatment arm should receive a preestablished second line as soon as they exhibit a clinical or radiologic progression. The determination of progression should be a clinical decision and not necessarily based upon RECIST (e.g., a patient with a 15% increase in measurable disease could have second-line therapy initiated without protocol deviation). As some patients will not proceed to second-line therapy, there must be clear documentation as to why this occurred. An economic analysis is also indicated. This analysis should be detailed and allow for extrapolation to different health care systems. In an era of growing concern about the financial costs of treatment to both the patient and overall health care system, it is important to evaluate whether the potential benefits of therapy are worthwhile. There is no question that the costs are substantial. The incremental costs for pemetrexed or erlotinib as maintenance therapy exceed the acceptability thresholds in some health care systems.[30–33] A suggested design of what we believe would be an appropriate switch-maintenance trial is provided in Fig. 2.

The issue with continuation maintenance is more straightforward. As we have discussed, the issue is duration of therapy. For nonsquamous carcinoma, a simple comparison of six cycles of treatment with platinum/pemetrexed followed

by observation versus four cycles of the same regimen followed by maintenance pemetrexed with similar assessments as described above (i.e., quality of life, economic analysis, etc.) is the simplest design. A third arm, evaluating continuation of pemetrexed after six courses of the doublet could also be considered.

What should be the endpoints for such trials? PFS is frequently employed as it allows for a faster time to event and therefore a shorter study. Furthermore, it is uncontaminated by subsequent therapies.[34] However, it is clearly inexact and subjective.[35] Prolongation of PFS has not always been associated with improvement of OS in lung cancer.[36] Realistically, the prolongation of time to event for OS versus PFS is unfortunately not all that long in advanced NSCLC. OS is an unequivocal and definitive endpoint suitable for drug appproval.[37] In addition, for the question of maintenance, and in particular, for switch maintenance, the issue of subsequent therapy is not truly relevant as the agents in question have already been established as effective and the question is whether there is actually a benefit to an earlier introduction of that agent.

CONCLUSIONS

Maintenance treatment subjects patients to the continuous toxicity and expense of chemotherapy. Quality-of-life analysis has not demonstrated even minimal benefit for either of the two strategies; a surprising finding, given the common assumption that delay of progression should result in improved quality of life.[8,17,38] The randomized trials purporting to show advantages for the use of switch-maintenance pemetrexed failed to provide the agent to patients randomized to the control arm, resulting in relatively few patients receiving the drug or an acceptable alternative. The question of switch-maintenance therapy is not one of treatment versus no treatment but rather of the early versus late introduction of a drug known to improve outcome. Despite statements by proponents that many patients on the control arm are unable to receive subsequent treatment, no data have been provided to support this position. For erlotinib, it is clear that virtually all benefit accrues to patients with activating EGFR mutations. There is little evidence to support the routine use of erlotinib as maintenance in patients without mutation and no evidence to support its use in patients who had response to initial treatment.

In summary, we believe that the issues discussed above raise serious questions regarding the adoption of switch-maintenance therapy for the routine treatment of all advanced NSCLCs. The issue of continuation maintenance is different and is really a question of the optimal duration of therapy. The recent results of the Phase III Study of Maintenance Pemetrexed (Pem) Plus Best Supportive Care (BSC) Versus Placebo Plus BSC Immediately Following Induction Treatment with Pem Plus Cisplatin for Advanced Nonsquamous Non-small Cell Lung Cancer (PARAMOUNT) study indicate that four cycles of platinum-based chemotherapy are likely insufficient for optimal benefit. Reexamination of the basis of that recommendation demonstrates that much of the evidence basis results from the cumulative toxicity of taxane therapy. Pemetrexed/cisplatin reduces the potential for neurotoxicity while the use of pemetrexed/carboplatin would essentially eliminate the potential for neurotoxicity (albeit with a possible reduction in efficacy compared with cisplatin) compared with a taxane based regimen. Current recommendations are for four to six cycles of treatment, and it seems that the greater number is optimal. It is unclear whether the benefits of indefinite continuation of maintenance therapy will be equal or superior to the benefits of six cycles of a platinum doublet. Practitioners must recognize that regulatory-agency approval of a drug for an indication does not mandate its use. This has been recognized in several guidelines that indicate that maintenance is an option, not a standard of care for all patients. It may very well be that selective use of maintenance in a subset of patients will be beneficial and appropriate. Only appropriately designed and independently conducted randomized studies can answer these questions.

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