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The SATURN trial: the value of maintenance erlotinib in patients with non-small-cell lung cancer

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Abstract

The first-line treatment of advanced non-small-cell lung cancer (NSCLC) generally consists of a maximum of six cycles of platinum-based doublet chemotherapy followed by surveillance for disease progression. Recently, the strategy of starting second-line treatment immediately following the completion of chemotherapy, known as 'maintenance' chemotherapy, has been investigated. The use of maintenance pemetrexed improves both progression-free and overall survival, while the use of maintenance docetaxel did not significantly improve overall survival. The Sequential Tarceva in Unresectable NSCLC (SATURN) study investigated the use of maintenance erlotinib following the completion of first-line chemotherapy. It demonstrated a significant improvement in overall survival from 11.1 months in the placebo group to 12.3 months in patients receiving maintenance erlotinib, with the important caveat that only 21% of patients in the placebo group ever received erlotinib. A subset of patients whose tumors had EGF receptor mutations had a higher magnitude of benefit from maintenance treatment. Therefore, maintenance erlotinib should be considered in the treatment of patients with NSCLC.

Keywords

EGF receptor tyrosine kinase inhibitor; erlotinib; gefitinib; maintenance chemotherapy; non-small-cell lung cancer

Lung cancer is the leading cause of cancer-related deaths worldwide. In 2004, lung cancer was the eighth most frequent cause of death, causing the deaths of an estimated 1.3 million people [1]. In the USA, an estimated 222,520 cases of lung and bronchus cancers will be diagnosed in 2010, and 157,300 people will die of this disease. Therefore, there is a large need for safer and more effective therapies for lung cancer [2].

Approximately 87% of lung cancer is comprised of non-small-cell lung cancer (NSCLC), with small-cell lung cancer comprising the remainder. More than half of NSCLCs are diagnosed after the cancer has reached an advanced stage, having spread outside the regional lymph nodes [3]. Treatment of metastatic NSCLC generally consists of platinum-based doublet chemotherapy for fit patients. The platinum component consists of either cisplatin, which is used more frequently in Europe, or carboplatin, which is used more widely in the USA. The second drug can consist of vinorelbine, a taxane (e.g., paclitaxel or docetaxel),

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gemcitabine or pemetrexed. All of these regimens appear to be approximately equivalent in efficacy [4,5]. In a subset of patients, the addition of the monoclonal anti-VEGF antibody bevacizumab to chemotherapy further improves overall survival [6]. Following completion of four to six cycles of chemotherapy, each being 3–4 weeks in length, patients generally enter a monitoring period without chemotherapy. At the time of disease progression, patients are administered single second-line agents with the goal of disease control. Despite the availability of improved chemotherapeutic agents, the median overall survival of patients with advanced NSCLC treated in the setting of clinical trials seldom exceeds 12 months, and these patients are not considered curable.

Recently, more active second-line chemotherapy has become available for the treatment of NSCLC, leading to a question of whether these agents would be more effective if moved to immediately follow the completion of the initial four to six cycles of platinum-based chemotherapy. This strategy, termed ‘early second-line’ or ‘switch maintenance’, and often just ‘maintenance’, has been tested with three drugs with proven activity in the second-line treatment of NSCLC.

The taxane docetaxel is US FDA-approved as a second-line treatment based on an improvement in median survival from 4.6 to 7 months compared with best supportive care ($p = 0.047$) [7]. However, when tested as a maintenance agent following cisplatin and gemcitabine first-line treatment, early docetaxel treatment did not significantly prolong overall survival compared with docetaxel at the time of progression. It did prolong progression-free survival (PFS; 5.7 vs 2.7 months; $p = 0.001$), and there was a trend toward overall survival benefit (12.3 vs 9.7 months; $p = 0.085$) [8]. Therefore, the use of maintenance docetaxel has not been widely adopted.

Pemetrexed, an antimetabolite, is FDA-approved for use in platinum-refractory NSCLC based on a noninferiority study that compared pemetrexed with docetaxel [9]. When it was tested in the maintenance setting following platinum-based chemotherapy, early pemetrexed treatment improved PFS from 2.6 to 4.3 months ($p < 0.0001$) and median overall survival from 10.6 to 13.4 months ($p = 0.012$) [10]. Based on this, pemetrexed was FDA-approved as a maintenance agent in 2009 for patients with nonsquamous NSCLC.

Erlotinib and gefitinib are small molecule EGF receptor (EGFR) tyrosine kinase inhibitors (TKIs). Four large frontline trials failed to demonstrate a survival advantage with the first-line use of either gefitinib or erlotinib in combination with chemotherapy [11–14]. However, in the BR.21 trial, 731 previously treated patients with NSCLC were randomized to receive erlotinib or best supportive care. Patients who received erlotinib had a median overall survival of 6.7 months compared with 4.7 months in those receiving best supportive care alone ($p < 0.001$), and also experienced an improvement in their quality of life, leading to FDA and EMA approval of erlotinib [15]. However, a similar trial using gefitinib did not result in significantly improved overall survival, which prompted the FDA to restrict the use of gefitinib to patients who had previously experienced clinical benefit [16]. In 2009, gefitinib was approved by the EMA for use in patients with NSCLC containing EGFR mutations based on two Phase III trials. In the Iressa Pan-Asia Study (IPASS), patients with EGFR mutations treated with first-line gefitinib compared with chemotherapy had a prolonged PFS (9.5 vs 6.3 months; hazard ratio [HR]: 0.48; 95% CI: 0.36–0.64; $p < 0.001$) [17]. In the Iressa NSCLC Trial Evaluating Response and Survival Versus Taxotere (INTEREST), second-line gefitinib treatment was shown to be noninferior to docetaxel in unselected patients, as measured by overall survival (7.6 months for gefitinib vs 8 months for docetaxel; HR: 1.020; 95% CI: 0.905–1.150) [18].

Based on the survival benefit of erlotinib in previously treated patients, there was interest in determining whether erlotinib treatment is more effective immediately following the completion of first-line chemotherapy. The Sequential Tarceva in Unresectable NSCLC (SATURN) trial was designed to investigate the effectiveness of maintenance erlotinib treatment until the time of progression, with the goal of prolonging overall survival and delaying disease progression [19].

Design

The SATURN trial is an international, multi-center, randomized, double-blind Phase III trial. Eligible patients had measurable, unresectable or metastatic NSCLC and were not allowed to have been previously treated with chemotherapy or EGFR inhibitors, or have uncontrolled brain metastases. Enrolled patients (n = 1949) were treated with the investigator's choice of one of seven standard chemotherapy regimens (without bevacizumab or pemetrexed) containing cisplatin or carboplatin plus a second agent. Following the completion of four cycles of chemotherapy, patients (n = 889) without disease progression, organ failure, intolerable toxicity or Eastern Cooperative Oncology Group (ECOG) performance status of two or higher were stratified by six factors (EGFR immunohistochemistry [IHC] status, chemotherapy regimen, disease stage, performance status, smoking history and geographic region) and then randomized into two groups. One group received erlotinib 150 mg daily (n = 438) and the other group received placebo and standard supportive care (n = 451) until disease progression, toxicity or death. Dose reductions were permitted in 50-mg decrements, as well as 2-week interruptions in treatment.

Data analysis

Tumor progression was determined using Response Evaluation Criteria In Solid Tumors (RECIST) criteria based on imaging at 6-week intervals until 48 weeks, then every 12 weeks thereafter, and quality of life was measured using the Functional Assessment of Cancer Therapy – Lung (FACT-L) questionnaire at the same intervals. Adverse and serious adverse events were scored using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) 3.0 criteria. The coprimary end points were PFS in all patients and PFS in patients with EGFR IHC-positive tumors.

Results

Baseline characteristics were well matched between the randomized groups. In the erlotinib- and placebo-treated groups, most patients were male (73 and 75%, respectively), Caucasian (84 and 83%, respectively), performance status 1 (69 and 68%, respectively), current or former smokers (83 and 83%, respectively), histology of either adenocarcinoma (47 and 44%, respectively) or squamous cell carcinoma (38 and 42%, respectively), had stable disease with chemotherapy (58 and 52%, respectively) and were EGFR IHC-positive (70 and 69%, respectively). The presence of EGFR-activating mutations, which are strongly associated with a response to EGFR TKI treatment [17], were identified in 5% of patients treated with erlotinib (22 patients) and 6% (29 patients) receiving placebo. Approximately 50% of both groups had an ‘indeterminate’ result on mutation testing analysis or insufficient tissue for testing.

In patients that received maintenance erlotinib, the tumor response rate was modestly better in patients treated with erlotinib versus placebo (11.9 vs 5.4%; p = 0.0006). PFS was significantly prolonged compared with patients treated with placebo (12.3 vs 11.1 weeks; HR: 0.71; 95% CI: 0.62–0.82; p < 0.0001) (Figure 1). The subset of patients with IHC-

positive tumors had a virtually identical magnitude of benefit, suggesting that this is not an important predictive factor in determining response to erlotinib. However, the few patients with documented EGFR-activating mutations that received erlotinib had a more impressive median PFS (~44 vs 14 weeks; HR: 0.10; 95% CI: 0.04–0.25; $p < 0.0001$) than patients without activating mutations (HR: 0.78; 95% CI: 0.63–0.96; $p = 0.0185$) (Figure 2). Most importantly, median overall survival was significantly prolonged in the group receiving erlotinib (12 months) versus placebo (11 months; HR: 0.81; 95% CI: 0.70–0.95; $p = 0.0088$) (Figure 3). In the small group of patients with activating EGFR mutations treated with erlotinib, median overall survival had not been reached, but 16 out of 24 patients in the placebo arm received subsequent erlotinib therapy, so there may not be an ultimate difference owing to extensive crossover.

Adverse events were experienced by 65% of patients receiving erlotinib and 20% of patients receiving placebo. Most events on the erlotinib arm consisted of grade 2 or milder rash (60%) or diarrhea (18%), which is consistent with previous studies. Only 16% of patients receiving erlotinib required a dose reduction compared with 3% receiving placebo. There was no difference in overall quality of life measurements between the two groups. In post-study treatments, EGFR TKI use was more frequent in the group that received placebo (21%) compared with the group that received erlotinib (11%).

Conclusion

The SATURN trial demonstrates that initiating erlotinib immediately following first-line chemotherapy results in improved survival compared with routine second-line therapy at the time of progression. Based on this study, the EMA and FDA both approved erlotinib in 2010 as a maintenance treatment for patients with NSCLC and stable disease after four cycles of standard chemotherapy.

One potential explanation for the effect of maintenance treatment is that the ‘switch maintenance’ treatment may simply allow patients to receive second-line therapy before symptomatic deterioration. Therefore, early second-line administration of erlotinib could be more effective in patients at risk of rapid symptomatic progression of their disease. However, one criticism of the methodology used in this study is that not all patients received second-line erlotinib – in fact, only 21% of the patients assigned to placebo received subsequent EGFR TKI. This may be a result of the trial design, which allowed unblinding and the use of second-line erlotinib in patients only if the investigator felt that there were no other viable treatment options. In addition, the use of EGFR TKI therapy may not have been prevalent owing to the expense of this treatment in many countries. Therefore, the observed survival benefit in this trial may simply reaffirm the results of BR.21: that erlotinib is an effective second-line therapy when administered to 100% of patients compared with 21% of patients, with all other treatments being relatively equal between the groups. The same phenomenon is apparent in the recent study of maintenance pemetrexed, in which substantially more patients received pemetrexed in the experimental group than in the placebo group [10]. Only the maintenance docetaxel trial was designed to allow a substantial proportion of placebo patients to receive docetaxel [8]. Interestingly, this study did have a higher absolute magnitude of improvement in both PFS and overall survival than the SATURN study, but both the smaller number of patients and the high degree of crossover may have precluded a significant benefit in overall survival (Table 1).

An additional study that provides more insight into the question of whether maintenance chemotherapy provides a benefit by bringing forward the timing of second-line therapy or simply providing access to active drugs is the recently reported French Intergroupe Francophone de Cancérologie Thoracique (IFCT)–Groupe Français de Pneumo-

Cancérologie (GFPC) 0502 study [20]. In this trial, patients who had stable disease after four cycles of cisplatin and gemcitabine were randomized to placebo, maintenance gemcitabine or switch maintenance erlotinib, with all patients planned to receive pemetrexed at the time of progression. In an early report of this trial, there was a significant improvement in PFS for patients that received either erlotinib (2.9 months; $p = 0.002$) or gemcitabine (3.8 months; $p < 0.0001$) compared with placebo (1.9 months). However, preliminary overall survival was not different between the groups, and all groups had more than 60% of patients receive pemetrexed as the next line of therapy. In total, these maintenance studies together suggest that switch maintenance treatments may simply prolong survival by providing increased access to effective second-line drugs.

One subgroup population in this study deserves special consideration. Patients with tumors harboring EGFR-activating mutations, predominantly exon 19 deletions or the *L858R* point mutation, are exquisitely sensitive to EGFR TKI treatment, as demonstrated most conclusively in a recent randomized trial of first-line gefitinib compared with chemotherapy [17]. Within the patients whose tumors could be analyzed for *EGFR* mutations, the *EGFR* mutation rate was approximately 10%, and these patients did very well when on erlotinib, with a median PFS over threefold higher in the erlotinib-treated patients. However, median overall survival was not reached in either group at the time of publication to determine superiority. Since these patients are so sensitive to EGFR TKI therapy and have a long disease natural history, it may be hard to determine whether early maintenance or delayed erlotinib is superior in terms of overall survival as most patients eventually had the opportunity to receive an EGFR TKI.

Future perspective

The use of a second-line chemotherapeutic should be considered immediately following first-line chemotherapy for patients with NSCLC and stable disease or a response to initial treatment. One alternative to this approach is to delay chemotherapy and closely monitor patients for progression, but it is often difficult to determine which patients are at risk of rapid progression. Indeed, over 50% of patients enrolled in the SATURN trial experienced disease progression on first-line chemotherapy and were never randomized at all. As symptomatic progression might preclude second-line chemotherapy entirely, a conversation with the patient about the benefits of maintenance chemotherapy versus the benefits of a drug holiday is appropriate.

Erlotinib, pemetrexed and perhaps docetaxel (which demonstrated PFS but not overall survival benefit) are potential current options for maintenance chemotherapy in this setting. However, as the use of pemetrexed is currently migrating into the frontline setting for patients with nonsquamous NSCLC, one outstanding question is whether continuing a relatively tolerable first-line agent such as pemetrexed as maintenance is equivalent to switching to a new second-line drug. The IFCT-GFPC 0502 study investigated this question using gemcitabine and suggests that there may at least be a PFS benefit to continuing a tolerable first-line drug in the maintenance setting.

Over the next few years, practice patterns are likely to shift in two ways. First, more tumors will undergo molecular testing to look for genetic changes in tumors. This information will help predict effective initial therapy, be it a targeted oral therapy such as erlotinib for EGFR-mutated tumors, crizotinib for tumors harboring *ALK* translocations [21] or chemotherapy, often with a VEGF inhibitor such as bevacizumab for adenocarcinomas. Given that earlier administration of second-line agents appears to potentially improve overall survival, it is also expected that practitioners will have a lower threshold to initiate changes in chemotherapy and may sequence treatments with fewer surveillance periods. Hopefully, an

individualized approach to treatment combined with the development of more effective agents will help maximize both the survival and quality of life for patients with this often rapidly progressive disease.

Acknowledgments

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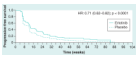

Figure 1. Kaplan–Meier estimate of progression-free survival in all patients in the SATURN trial
HR: Hazard ratio.

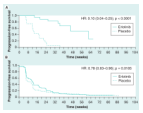

Figure 2. Kaplan–Meier estimate of progression-free survival in mutant EGF receptor subsets of patients in the SATURN trial

(A) EGF receptor mutation-positive tumors. **(B)** EGF receptor mutation-negative tumors. HR: Hazard ratio.

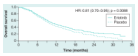

Figure 3. Kaplan–Meier estimate of overall survival in all patients in the SATURN trial
HR: Hazard ratio.

Table 1

Comparison of randomized controlled trials involving switch maintenance therapy

Trial	Comparison	Patients (n)	PFS (months)	p-value/HR (95% CI)	OS (months)	p-value/HR (95% CI)	Patients receiving maintenance drug (%)	Ref.
Fidias *et al.*	Immediate docetaxel	153	5.7†	0.001	12.3	0.085	95	[8,22]
	Placebo then delayed docetaxel	156	2.7		9.7	HR: 0.80	63	
JMEN	Pemetrexed	441	4.3†	<0.0001	13.4†	0.012	98 + 1‡	[10]
	Placebo	222	2.6	HR: 0.50 (0.42–0.61)	10.6	HR: 0.79 (0.65–0.95)	18	
SATURN	Erlotinib	437	2.8†	<0.001	12.0†	0.009	NR + 11‡	[19]
	Placebo	447	2.6	HR: 0.71 (0.62–0.82)	11.0	HR: 0.81 (0.70–0.95)	21	
IFCT-GFPC 0502	Gemcitabine	149	3.8†	<0.0001 HR: 0.55 (0.43–0.70)	12.1	HR: 0.86 (0.66–1.12)	60 (pemetrexed)	[20]
	Erlotinib	155	2.9†	0.002 HR: 0.82 (0.73–0.93)	11.8	HR: 0.91 (0.80–1.04)	63	
	Placebo	152	1.9		10.7		76	

† Statistically superior result.

‡ Treatment on trial plus post-study treatment.

HR: Hazard ratio; IFCT-GFPC: Intergroupe Francophone de Cancérologie Thoracique – Groupe Français de Pneumo-Cancérologie; NR: Not reported; OS: Overall survival; PFS: Progression-free survival; SATURN: Sequential Tarceva in Unresectable NSCLC.