MINI REVIEW

Clinical significance of post-progression survival in lung cancer

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Abstract

Progression-free survival (PFS) and overall survival (OS) are two common endpoints in cancer trials. OS is usually preferred, because it is reliable, precise, meaningful, and can easily be documented. However, subsequent lines of therapy might confound the effects of first-line treatment on OS. Whether PFS or OS is the more appropriate endpoint in clinical trials of metastatic cancer remains controversial. Previous reports on lung cancer have shown that an increase in PFS does not necessarily result in an increase in OS; however, post-progression survival (PPS) is strongly associated with OS after early-line treatment. The significance of PPS after first and second-line therapy at the individual level in patients with advanced lung cancer has also recently been reported. Findings of previous reports indicate that PPS is highly associated with OS after first and second-line chemotherapy in patients with advanced non-small cell lung cancer and small cell lung cancer, whereas PFS is only moderately associated with OS. Therefore, subsequent treatment after disease progression following early-line treatments may greatly influence OS. This review demonstrates that even in advanced lung cancer, PPS, rather than PFS, has become more strongly associated with OS over the years, potentially because of intensive post-study treatments. As a result of the increasing impact of PPS on OS, a PFS-related advantage does not necessarily indicate an OS-related advantage. Thus, the prolongation of PPS might limit the classical role of OS for assessing true efficacy derived from early-line chemotherapy in future clinical trials.

Introduction

Chemotherapy agents may be used for the treatment of active, clinically apparent cancer.[1] Over the past 15 years, significant progress has been achieved in the systemic treatment of advanced cancers, including that of lung cancer, the leading cause of cancer-related death worldwide.[2] Most individuals with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) have metastatic disease at the time of diagnosis and therefore have a poor prognosis. The introduction of novel chemotherapeutic agents, as well as the use of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), anaplastic lymphoma kinase (ALK)-tyrosine kinase inhibitors, bevacizumab and ramucirumab, and programmed death-1 (PD-1) antibodies have improved the outlook for patients with advanced lung cancer. The growing number of potentially active drugs and drug combinations against advanced lung cancer and the possibility of testing novel therapies in different treatment lines are transforming the development of novel therapies into an increasingly more complex endeavor, and one in which the choice of study endpoints is progressively more critical. In addition, the growing number of options has led to increasingly more complex decision-making for clinicians, who are now faced with the need to distinguish between clinical trial endpoints and therapeutic objectives for their patients.

Progression-free survival (PFS) and overall survival (OS) are two common endpoints in cancer trials. OS is usually preferred, because it is reliable, precise, and meaningful, and can easily be documented by noting the date of

death. However, subsequent lines of therapy might confound the effect of first-line treatments on OS.[3] In contrast, as PFS measurement is quicker and more convenient, it may be easier to assess than OS.[4] If there is a strong correlation between PFS and OS, PFS may serve as a surrogate endpoint for OS. In NSCLC, an increase in PFS does not necessarily result in an increase in OS;[5] however, post-progression survival (PPS) is strongly associated with OS after first-line treatment.[6,7] The evaluation of PPS using a simple method was first reported in 2009, whereby OS was expressed as the sum of PFS and PPS (Fig 1).[3] In recent years, as for breast, ovarian, colorectal, gastric, and renal cell cancers, a growing number of active compounds are available for second or third-line chemotherapy for advanced NSCLC and SCLC.[8–12] Therefore, subsequent treatment after disease progression following first-line chemotherapy may greatly influence OS.

At the individual or trial level, the effect of therapies administered after disease progression on survival is of high interest. Previous reports have shown that PPS after first and second-line chemotherapy for advanced gastric cancer and after third-line chemotherapy for metastatic breast cancer highly correlated with OS at the individual level.[13–15] The significance of PPS after first and second-line therapy at the individual level in patients with advanced lung cancer has also been reported.[16–24] Therefore, an overview of PPS after early-line therapy in patients with cancer using individual-level data might be of clinical importance. We focused our review on the current evidence regarding the use of PPS in lung cancer.

Significance of progression-free and overall survival

Whether PFS or OS is the more appropriate endpoint in clinical trials of metastatic cancer remains controversial.[3,25–29] In some disease and treatment settings, an improvement in PFS does not necessarily result in improved OS.

In cancer drug development, the overall response rate is usually assessed as an indicator of activity in phase II trials, while randomized phase III trials rely on other endpoints, such as PFS.[30] PFS is defined as the time elapsed between treatment initiation and tumor progression or death from any cause, with censoring of patients who are lost to follow-up.[30] Many recent randomized trials on solid tumor oncology have utilized PFS as the primary endpoint. In addition, several trials have also used time to tumor progression (TTP) as the primary endpoint, with TTP differing from PFS in that the events of interest are only disease progression[31] and, in some studies, death resulting from malignancy.[32] Historically, both PFS and TTP have often been accepted as markers of clinical benefit for drug approval.[33] For regulatory purposes, PFS may be preferable to TTP as it also captures fatal toxicity, while TTP is unconfounded by deaths unrelated to cancer.[34]

Given its objectivity and the unquestionable benefit derived by patients, OS has historically been considered the most important endpoint in medical oncology.[34] However, OS has also been shown to be an elusive endpoint; although it is objective and simple to measure, it has the disadvantage of requiring extended patient follow-up and of being confounded by causes of mortality unrelated to cancer. Furthermore, as novel therapies are shown to be effective along the treatment continuum, patient survival may be influenced by the use of such therapies after participation in a given trial.[35,36] In the latter scenario, there is frequent crossover to the agent under investigation, thus obscuring the effect of treatment on OS. As a result of these various factors, many randomized trials are grossly underpowered to detect plausible OS differences.[37] Other time-dependent endpoints on the basis of tumor assessment are available for use in drug development, and many of them are undergoing validation either as surrogate endpoints, or as indicators of clinical benefit. Defined as the time from randomization to death, OS has been considered the gold standard of clinical trial endpoints. In part, this is because it is unambiguous and does not suffer from interpretation bias. An additional advantage of the survival endpoint is that it can balance the effect of therapies with high treatment-related mortality, even if tumor control is substantially better with the new treatment. However, there is concern that because patients may receive multiple lines of therapy following a clinical trial, the results may be confounded by those subsequent therapies. The latter concern is often cited as the reason why an advantage in PFS
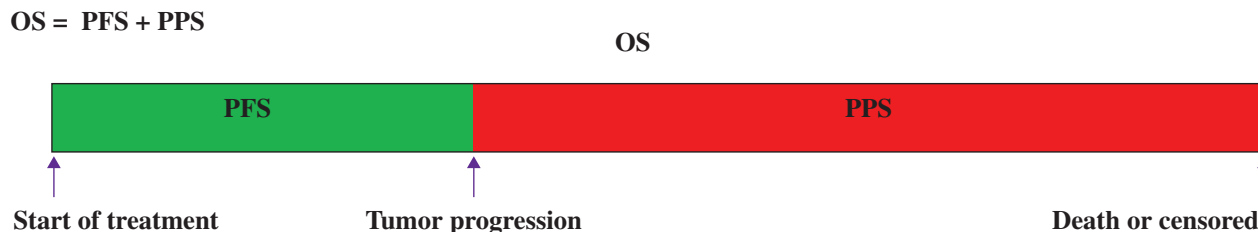
OS = PFS + PPS

Figure 1 Concept of post-progression survival (PPS). OS, overall survival; PFS, progression-free survival.

disappears when one looks to OS. However, as a review of clinical trials confirmed, only the statistical validity disappeared, not the magnitude.[30]

Although convincingly demonstrated favorable effects on OS are the most significant outcome of a clinical trial, there is scope for discussion regarding the role of PFS in clinical trials. PFS is applied both as a surrogate end-point for OS and as a primary trial end-point in itself, the latter of which has been used in an increasing number of cancer clinical trials. Robinson *et al.* reported that PFS is now the most common basis for granting approval of an indication.[38] Regulatory agencies consider PFS as a surrogate end-point for regular approval; it is thus clear that PFS gains are relevant to decisions concerning new drug approval, and clinical trials will continue to use it as a primary end-point in various settings.

Clinical significance of post-progression survival (PPS)

Given its objectivity and the benefits derived by patients, OS has been historically considered the most important therapeutic objective in advanced NSCLC, whereas PFS captures tumor shrinkage, tumor stabilization, and their duration, all of which are essential for the evaluation of new target agents.[4] However, with the currently increasing number of aforementioned factors, the effects of subsequent therapies may potentially affect the advantage of OS over PFS.

To date, few studies have addressed whether survival after progression to first-line chemotherapy has substantially improved over the years and to what degree PPS correlates with OS. PPS was first reported in 2009 with the use of a simple device.[3] Broglio and Berry recently focused on PPS, which they termed survival post-progression, defined as OS minus PFS, in a hypothetical clinical trial setting under the assumption that there was a treatment difference in PFS, but not in PPS.[3] Here, the standard definition of "progression" included death from any cause, and therefore the progression event may be death. As the median PPS increased, the probability of detecting a statistically significant difference in OS decreased substantially. Even for a trial with an observed *P* value for improvement in PFS of 0.001 (whereas there was a >90% probability for statistical significance of the difference in OS if the median PPS was two months), this probability decreased to only ~50% if the median PPS was six months.[3]

Several reports have assessed the association between PPS and OS in trials of advanced NSCLC, as well as advanced breast, ovarian, colorectal, gastric, and renal cell cancers.[6–12,39,40] The trial level studies that addressed the correlation between OS and PFS or PPS of various cancers are summarized in Table 1. For example, Hayashi *et al.*

concluded that the median OS was highly associated with the median PPS but not with the median PFS (Spearman's rank correlation coefficient, $r = 0.94$ and 0.51, respectively), and that there was only a weak association between the treatment benefits for PFS and OS (Spearman's rank correlation coefficient, $r = 0.29$) for patients with advanced NSCLC who received second or third-line chemotherapy.[7,39] A similar result was reported for patients with advanced NSCLC and advanced gastric cancer.[6,11] The explanation for these conclusions was that the average median PPS was longer than the average median PFS. In other words, the ratio of PPS/OS was higher than that of PFS/OS.

However, the analyses described above were performed with abstracted data, which cannot be used to predict an individual's chance of survival. The use of individual patient data might allow better characterization of the relationship between OS and other endpoints based on tumor assessment, including PFS and PPS. Recently, the significance of PPS after first and second-line therapy at the individual level in patients with advanced lung cancer has been reported.[16–24] Although there have been reports about PPS after EGFR-TKI and ALK-TKI treatment at the individual level in patients with advanced EGFR-mutated and ALK rearrangement positive NSCLC, those reports did not address the correlation between OS and PFS or PPS.[41–43] Studies that did address these correlations are summarized in Table 1. In all studies, PPS was strongly associated with OS, whereas PFS was moderately correlated with OS. In multivariate Cox regression analysis, studies of first-line treatment based on individual advanced non-squamous NSCLC with unknown oncogenic driver mutations revealed that long PPS was associated with performance status (PS) at the beginning of second-line treatment, the best response at the second-line treatment, and the number of regimens after progression beyond first-line chemotherapy.[16] Studies of second-line treatment based on individual advanced non-squamous NSCLC with unknown oncogenic driver mutations revealed that long PPS was associated with the PS at the end of second-line treatment, the best response at the third-line treatment, and the number of regimens after progression beyond second-line chemotherapy.[19,20] Studies of first-line treatment based on individual patients with advanced NSCLC harboring sensitive EGFR gene mutations revealed that long PPS was associated with the best response at second-line treatment, and the number of regimens after progression beyond first-line chemotherapy.[17] Studies of first-line single agent chemotherapy based on individual elderly patients (aged 75 or older) with advanced NSCLC revealed that long PPS was associated with clinical stage (stage III/IV), and PS at the end of first-line treatment.[18] Furthermore, studies based on individual limited-disease SCLC patients treated with first-line

Table 1 Studies on the correlation of OS with PFS and PPS in lung cancer

Objective (references)	Number	Correlation with PFS-OS	Correlation with PPS-OS	Independent prognostic factors for PPS
NSCLC				
First-line				
Non-sq. NSCLC 1st-line[16]	50	$r = 0.67$, $P < 0.05$, $R^2 = 0.39$ Moderate	$r = 0.89$, $P < 0.05$, $R^2 = 0.79$ Strong	PS at the beginning of second-line treatment
				Best response at second-line treatment
				Number of subsequent treatments
EGFR positive NSCLC 1st-line[17]	35	$r = 0.13$, $P = 0.45$, $R^2 = 0.001$ Weak	$r = 0.85$, $P < 0.05$, $R^2 = 0.86$ Strong	Best response at second-line treatment
				Number of subsequent treatments
Elderly NSCLC 1st-line[18]	58	$r = 0.72$, $P < 0.05$, $R^2 = 0.41$ Strong	$r = 0.73$, $P < 0.05$, $R^2 = 0.76$ Strong	Clinical stage
				PS at the end of first-line treatment
Second-line				
Non-sq. NSCLC 2nd-line[19]	39	$r = 0.76$, $P < 0.05$, $R^2 = 0.50$ Strong	$r = 0.90$, $P < 0.05$, $R^2 = 0.85$ Strong	Best response at third-line treatment
				Number of subsequent treatments
Non-sq. NSCLC 2nd-line[20]	86	$r = 0.50$, $P < 0.05$, $R^2 = 0.21$ Moderate	$r = 0.86$, $P < 0.05$, $R^2 = 0.93$ Strong	PS at the end of second-line treatment
				Number of subsequent treatments
SCLC				
Limited-disease SCLC CRT[21]	71	$r = 0.46$, $P < 0.05$, $R^2 = 0.38$ Moderate	$r = 0.86$, $P < 0.05$, $R^2 = 0.72$ Strong	Best response at second-line treatment
				Presence of distant metastases at recurrence
				Number of subsequent treatments
Extensive-disease SCLC 1st-line[22]	49	$r = 0.58$, $P < 0.05$, $R^2 = 0.24$ Moderate	$r = 0.97$, $P < 0.05$, $R^2 = 0.94$ Strong	Best response at second-line treatment
				Number of subsequent treatments
Extensive-disease SCLC 1st-line[23]	63	$= 0.72$, $P < 0.05$, $R^2 = 0.62$ Strong	$= 0.90$, $P < 0.05$, $R^2 = 0.71$ Strong	Type of relapse (Refractory/sensitive)
				Number of subsequent treatments
Elderly extensive-disease SCLC 1st-line[24]	57	$r = 0.76$, $P < 0.05$, $R^2 = 0.25$ Strong	$r = 0.92$, $P < 0.05$, $R^2 = 0.83$ Strong	Best response at second-line treatment
				Number of subsequent treatments

The *r* values represent Spearman's rank correlation coefficient. The R^2 values represent linear regression. EGFR, epidermal growth factor receptor; non-sq., non-squamous; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; PS, performance status; sq, squamous cell carcinoma; SCLC, small cell lung cancer.

chemoradiotherapy revealed that long PPS was associated with the best response at second-line treatment, the presence of distant metastases at recurrence, and the number of regimens after progression beyond first-line chemotherapy.[21] Studies based on individual extensive disease (ED)-SCLC patients treated with cisplatin plus irinotecan revealed that long PPS was associated with the best response at the second-line treatment and the number of regimens after progression beyond first-line chemotherapy.[22] Studies based on individual ED-SCLC patients treated with carboplatin plus etoposide revealed that long PPS was associated with type of relapse (refractory/sensitive) and the number of regimens after progression beyond first-line chemotherapy.[23] Studies based on individual

elderly patients with ED-SCLC treated with carboplatin plus etoposide revealed that long PPS was associated with best response at second-line treatment and the number of regimens after progression beyond first-line chemotherapy.[24] Overall, these findings suggest that in most of the previous studies at the individual level, best response at subsequent treatment and the number of regimens after progression beyond first or second-line chemotherapy independently affected PPS. These findings indicate that patients are also likely to be able to continue chemotherapy and achieve prolonged PPS, which is associated with a longer OS. Therefore, we have to control factors that affect PPS. The number of treatment regimens employed following disease progression after first or second-line

chemotherapy probably reflects the increasing number of available drugs, such as pemetrexed, S-1, EGFR-TKIs, ALK-TKIs, bevacizumab and ramucirumab, programmed death ligand-1 (PD-L1) antibody, amrubicin, irinotecan, and topotecan, which are available as second or third-line chemotherapy for advanced NSCLC and SCLC. The association between OS and PPS has become closer over the years, as observed by Hotta *et al.* (coefficient of determination; r^2 = 0.4428, 0.7242, and 0.9081 in 1988–1994, 1995–2001, and 2002–2007, respectively).[6] Longer PPS might be associated with several clinical situations, including first-line use of molecular-targeting agents.

In contrast with the findings of previous studies,[44,45] some reports of individual levels did not find PFS to be a surrogate endpoint for OS in advanced lung cancer patients,[16–24] although PPS was not evaluated in those studies. These reports found that PFS was much shorter than PPS. Thus, PPS was closely related to OS – in fact, the relationship was linear.[16–24] The fact that PPS accounted for the majority of OS suggests that the chemotherapy used was not sufficiently effective for PFS to be a significant component of OS. In diseases with dismal prognoses such as advanced NSCLC and SCLC, there is no doubt that OS should remain the primary endpoint for demonstration of efficacy, both in first and subsequent lines. From this point of view, the relevance of the analysis of correlation of PFS and PPS with OS is not substantial for the design of clinical trials, compared to other solid tumors characterized by a longer life expectancy and by the availability of a higher number of effective treatment lines. Thus, in clinical trials where patients are expected to have a short PFS after first or second-line chemotherapy, such as those with advanced NSCLC and SCLC, factors that affect PPS need to be considered.

Problems associated with PPS

Many important questions remain, including what is the impact of maintenance therapy on the relationship between PFS and PPS. Our review did not address this question, although some studies that incorporated maintenance therapy, such as a report written by Pfisterer *et al.*[46] met the inclusion criteria of the review and were included in the analysis. Analysis of maintenance trials specifically, as well as investigating the effect of targeted therapies on this relationship, would add useful insight.

An increase in median PPS accompanying an increase in median OS was apparent in recent trials of patients with advanced lung cancer compared to older trials. Currently, OS is accepted as the gold standard for efficacy evaluation in phase III trials for advanced lung cancer. However, as PPS increases, OS can become skewed, and a statistically significant benefit in terms of PFS will likely become masked with OS as the endpoint.[3]

The sample size of the analysis for PPS at the individual level was relatively small. These results should therefore be validated in larger populations.

Evaluation of PFS as a surrogate endpoint for OS has often been conducted by quantifying the strength of the association between these endpoints at the individual level (referred to as individual-level surrogacy), and of that between the effects of treatment on these endpoints (trial-level surrogacy).[47–50] Previous reports of the correlation between PFS and OS were not an exercise in surrogate validation because of the lack of investigation into the correlation between the effects of chemotherapy on these endpoints. However, these reports have yielded the key finding that PPS, not PFS, is highly associated with OS at the individual level. Individual-level data, as described above, are not necessarily linked to trial-level data, and therefore cannot always be used to predict a trial's chance of survival on the basis of PFS or PPS shown here. PPS is also a sum of each PFS in each treatment line conducted after first-line treatment. For these reasons, initiating a treatment that can confer longer PFS may result in longer PPS and OS. From this point of view, PFS may still serve as an important endpoint in both clinical trials and practice. We need to have a better understanding of whether delaying progression for short periods confers any meaningful patient benefit in terms of control or delay in progression of disease-related symptoms.

Summary and future development of PPS

Findings of previous reports indicate that PPS is highly associated with OS for first and second-line chemotherapy in patients with advanced NSCLC and SCLC, whereas PFS is only moderately associated with OS. Therefore, subsequent treatment after disease progression following first and second-line treatments may greatly influence OS. OS remains an appropriate endpoint of clinical trials for chemotherapy-naive patients with advanced NSCLC and SCLC. Given the great effect of PPS on OS, we propose a precise assessment of clinical course after disease progression in each clinical trial.

In most of the previous individual level studies, the number of regimens after progression beyond first or second-line chemotherapy independently affected PPS. These findings suggest that relaying to subsequent treatment without becoming exhausted by early-line treatments might be important. Subsequent lines of therapy play a major role in determining OS in advanced NSCLC and SCLC, and further studies are required to understand the role of PFS versus PPS in determining OS, especially when first-line PFS has not been convincingly demonstrated as a good surrogate for OS in this disease.

The average proportion of median OS accounted for by median PPS significantly increased in recent trials compared to older trials. According to recent studies, chemotherapy sensitivity greatly affects OS. Therefore, the choice of drugs should be decided based on whether the patient is chemotherapy-sensitive or not. The recent prolongation of PPS is likely the result of the increasing number of active compounds being administered appropriately. One trial from a decade ago, when pemetrexed and EGFR-TKIs were not available, reported that only ~20% of patients received second-line chemotherapy.[51] The recent widespread use of active second and third-line therapies thus appears to have contributed to the prolongation of PPS in patients with advanced lung cancer. Many factors other than more effective treatments could be contributing to prolonged survival in trials of advanced lung cancer patients. Consequently, prolongation of PPS might contribute to OS prolongation. Moreover, subsequent treatment, such as PD-L1 antibody, docetaxel plus ramucirumab, and osimertinib could be important hereafter. Although no reports on PPS for advanced squamous cell lung cancer, locally advanced NSCLC, relapsed SCLC, and lung cancer treated with PD-L1 antibody, among others, have been published, the significance of PPS in these patients might reflect the previous reports. Further research is warranted to evaluate the impact of PPS on OS, using individual data from a larger number of patients.

In conclusion, this review demonstrated that even in advanced NSCLC and SCLC, PPS rather than PFS has become more strongly associated with OS over the years, potentially because of intensive post-study treatments. As a result of the increasing impact of PPS on OS, even in advanced NSCLC and SCLC, a PFS-related advantage does not necessarily indicate an OS-related advantage. Thus, the prolongation of PPS might limit the classical role of OS for assessing true efficacy derived from early-line chemotherapy in future clinical trials.

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