Correlation of progression-free and post-progression survival with overall survival in advanced colorectal cancer

F. Petrelli* & S. Barni
Oncology Unit, Azienda Ospedaliera di Treviglio, Treviglio, Italy

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Background: Polychemotherapy and biological drugs have increased therapeutic options and outcomes of advanced colorectal cancer (CRC). We examined the relation between progression-free survival (PFS), post-progression survival (PPS) and overall survival (OS) in trials of modern (oxaliplatin- and irinotecan-based) chemotherapy alone or with targeted therapies for advanced CRC. We also evaluated surrogacy of PFS and OS.

Patients and methods: A PubMed search identified 34 randomized trials. We split the OS, PFS and PPS and evaluated the correlation between OS and either PFS or PPS.

Results: The median PPS and PFS were 10.75 and 8.4 months, respectively. For all trials, PPS was strongly associated with OS [regression coefficient ($R^2$) = 0.8; Spearman’s rank correlation coefficient ($r$) = 0.88], whereas PFS was moderately associated with OS ($R^2$ = 0.43; $r$ = 0.64). In trials with targeted therapies, the correlation of PPS with OS was 0.88. However, across all trials, correlation between differences in median PFS ($Δ$PFS) and median OS ($Δ$OS) is 0.59 ($P = 0.0007$), confirming PFS/OS surrogacy.

Conclusion: Our findings indicate that in recent first-line, phase III, trials, OS becomes more associated with PPS than PFS. However, improvements in PFS are strongly associated with improvements in OS. In this setting so, PFS may be an appropriate surrogate for OS.

Key words: advanced colorectal cancer, chemotherapy, correlation, overall survival, phase III trials, post-progression survival

introduction

For the majority of metastatic colorectal cancer (CRC) patients, the treatment consists of fluoropyrimidine-based systemic polychemotherapy. The aims of treatment—except for patients with liver- (or lung-) limited disease amenable to surgical resection—are palliation, prolongation of survival and maintenance of quality of life. When 5-fluorouracil (5-FU) was the only available active agent, overall survival (OS) in phase III trials was ~11–12 months. In the modern era, the average median OS has reached about 2 years, in particular for patients enrolled in controlled trials with biologics [1]. However, ~10% of patients survive at 5 years [2]. This increase has been mainly driven by the availability of new active agents [3]. Fluoropyrimidine-based polychemotherapy (including oxaliplatin and irinotecan, eventually associated with monoclonal antibodies (MoAbs) as bevacizumab, cetuximab or panitumumab) is now the cornerstone of treatment in first-line settings. For stage IV CRC, the availability of all active drugs during the course of the disease has been strongly correlated with OS in large phase III trials over the last decade [4]. Because of the survival benefits from second- and beyond lines of chemotherapy, the routine practice of crossover in clinical trials severely limits the ability to detect an OS advantage of one treatment regimen over another, particularly in first-line settings. Therefore, the activity of a new agent or combination regimen is better captured by the progression-free survival (PFS). Improvements in PFS correlate with longer survival in major phase III studies [5, 6] and are not affected by subsequent therapies that influence post-progression survival (PPS). This concept has been recently explored both in breast cancer and in non-small-cell lung cancer [7–9]. Addressing PPS and subsequent treatments is important in understanding survival benefit of new drugs. A PFS benefit, in general, does not imply improvement in OS, particularly for diseases with long median PPS. In particular, in breast cancer, OS is a reasonable primary end point when median PPS is short, but is unreliable when median PPS is long (e.g. >12 months [9]). The hypothetical prolongation of PPS could dilute any OS benefit obtained with first-line chemotherapy in modern randomized clinical trials. The association PPS/OS has not been clearly
explored in advanced CRC trials, in particular in phase III trials with biological agents published in last decades. In first-line settings, for example, the addition of cetuximab moderately increased the median OS when added to irinotecan but not to oxaliplatin-based chemotherapy in Kirsten rat sarcoma 2 viral oncogene homolog (KRAS) ‘wild-type’ population [1, 10]. Similarly, the anti-vascular endothelial growth factor (VEGF) MoAb bevacizumab, when given upfront, increased median OS when added to irinotecan but not to oxaliplatin-based schedules [11, 12].

The effect of subsequent therapies instituted after disease progression on median OS in clinical trials is thus of interest. In the present review, we split OS of modern phase III trials for chemotherapy-naïve patients with CRC into PFS and PPS and assessed the association of each with OS. The evaluation of PFS surrogacy of OS was also performed.

methods

search strategy and selection of trials

A search for PubMed citations until 4 March 2012 was carried out. Key words included in the search were ‘colorectal cancer or colorectal carcinoma’, and ‘advanced or metastatic’. The search was limited to randomized, controlled trials and articles published in English. We reviewed each publication, and phase III studies that compared two or more, modern, first-line systemic chemotherapies (including treatment with molecularly targeted agents) for advanced or metastatic CRC were selected. To find any additional trials, we searched the reference lists of included trials and of large systematic reviews. We included trials that provided data for both OS and either PFS or time to progression (TtP), whether or not these parameters were explicitly defined.

Inclusion criteria were also: (i) the combination of 5-FU (or capecitabine, S1 or uracil/tegafur) with irinotecan and/or oxaliplatin and/or Mytomycin C with or without a MoAb (bevacizumab, cetuximab or panitumumab) in at least one study arm; (ii) clinical phase III trials and (iii) first-line trials only. Trials were excluded if they investigated: (i) targeted agents alone or in association (without chemotherapy) because this is not the standard of care as first-line therapy in stage IV disease, (ii) other experimental biological agents (in addition to chemotherapy) because not approved for CRC, (iii) other forms of chemotherapy administration other than the standard intravenous and other unconventional dose of drugs (e.g. regional infusion or chronomodulated) or (iv) they included other forms of regional treatment as radiotherapy because they could confound the efficacy of systemic agents. To avoid the bias, the authors independently abstracted the data from the trials.

data abstraction and clinical endpoints

Two end points (PFS and TtP) based on tumor assessment are collectively referred to as PFS in the present analysis, similar to the approach adopted in recent reports [13, 14]. Median OS and median PFS were extracted from all trials that provided data for each treatment group. Median PPS was defined as median OS minus median PFS for each trial. We also obtained the following information from each report: year of publication of trial, number of patients randomized, number of patients in each treatment arm, number of treatment arms in each trial and type of agents. Due to the approval of cetuximab and panitumumab in KRAS wild-type patients, analysis was restricted to those patients if available in the text.

The end points of this analysis were: (i) to quantify the correlation of PFS and PPS with OS in phase III first-line trials in metastatic CRC, through linear correlation, (ii) to evaluate if these correlation changed according to the period of publication of trials (before and after the year 2005), (iii) to evaluate (and quantify) if these correlations are different for chemotherapy only and chemotherapy + biological agents arms, (iv) to correlate differences in median PFS and OS in each trial to evaluate the surrogacy of PFS with respect to OS.

data analysis

We summarized the survival data (median OS, median PFS, median PPS, differences in median PFS and median OS of control and experimental arms) as the median for all trial arms. To assess the relation between median OS and either median PFS or median PPS, we used a coefficient of correlation ($R^2$) and Spearman’s rank correlation coefficient. To account for differences in sample size and patient’s characteristics among trial arms, we weighted all analyses by the number of patients in each arm and by the rate of good performance status of included subjects. In addition, all trials were divided into two groups on the basis of the use of MoAbs in addition to chemotherapy. Further, all trials were divided into two groups on the basis of period before or after the year 2005 to evaluate a possible change in PPS, and we assessed whether the evaluated relations might be dependent on the year of release of the biological agents data. We also calculated the differences of PFS between experimental and control arms ($\Delta$PFS) in each trial and correlated them with the differences in median OS derived from the same arms ($\Delta$OS) to evaluate the surrogacy PFS/OS. The differences in OS ($\Delta$OS) and in surrogate end point ($\Delta$PFS) were calculated as the median estimate in the experimental arm(s) minus the median estimate in the control arm. The Spearman’s rank correlation coefficient ($r$) was used as a measure of correlation between the differences in PFS and the difference in OS.

All reported $P$-values correspond to two-sided tests, with $P$-values <0.05 considered statistically significant. Analyses were carried out with NCSS 2007 version 07.1.20 software (released 19 February 2010; www.ncss.com).

results

characteristics of the trials

Our search yielded a total of 1072 potentially relevant publications. Initially, 1046 studies were excluded for at least one of the following reasons: they included old agents no longer used in clinical practice (e.g. interferon) or two MoAbs (both exclusion criteria); they examined other malignancies or combined modality treatments (e.g. radiotherapy); they were not randomized; they were phase I or II trials; they were review articles, letters or commentaries; they represented the subgroup analyses of other trials or they were the duplicates of similar retrieved studies. The selection process for the randomized, controlled trials is shown in Figure 1. The review of the remaining 36 publications yielded 34 trials (with 65 arms) that were considered to be highly relevant for the present study [1, 10–12, 15–47]. Seventeen arms were finally excluded from the present analysis: $n = 12$ including monotherapy arms (including 5-FU or capecitabine or irinotecan alone), $n = 2$ arms including not conventional, first-line agents as raltitrexed and methotrexate, $n = 2$ arms including bevacizumab + panitumumab- and bevacizumab + cetuximab-based chemotherapies and $n = 1$ arm containing chemotherapy + panitumumab (not yet approved combination). The main characteristics of the 34 phase III trials included in this analysis are listed in Table 1. A total of 16 408 patients with advanced CRC were enrolled, with a median number of...
patients per study of 205 (range 41–815). All trials had a prevalent proportion of colon adenocarcinoma. Twenty-three trials randomly assigned patients to different chemotherapy arms, while 11 trials randomized patients to chemotherapy with or without a MoAb (bevacizumab, cetuximab or panitumumab).

median OS, PFS and PPS in all trials, in subgroups based on the use of MoAbs and in trials published before and after 2005

The median OS was 19 months, while the median PFS and PPS were 8.4 and 10.75 months, respectively for all arms (arms \( n = 65 \); ratio PPS/OS 56%). For the chemotherapy-only arms (\( n = 49 \)), the median OS, PFS and PPS were 18.9, 8 and 10.4 months, respectively. For arms including biological agents in addition to chemotherapy (\( n = 16 \)), the median OS, PFS and PPS were 20.5, 9.4 and 11.8 months, respectively. In arms published before and after 2005, the median OS, PFS and PPS were 17.4, 7.6, 9.55 and 18.9, 8.2, 10.8 months, respectively.

relation between OS and either PFS or PPS

The relation between median OS and either median PFS or median PPS for the 65 treatment arms of all trials is shown in Figures 2A and 3A, respectively. We found that median PPS was strongly associated with median OS (\( R^2 = 0.80 \) and \( r = 0.88, P < 0.0001 \)) on the basis of Spearman’s correlation coefficient, whereas median PFS was more moderately correlated with median OS (\( R^2 = 0.43 \) and \( r = 0.64, P < 0.0001 \)). This means that the percentage of variation in median OS that can be accounted for by variation in PPS and PFS is 80% and

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**Table 1.** Characteristics of the 34 trials included in the analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of arms/total randomized patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of trials/arms/total randomized patients</td>
<td>34/65/16 408</td>
</tr>
<tr>
<td>Median number of patients</td>
<td>205 (range 41–815)</td>
</tr>
<tr>
<td>Number of trial arms</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Chemotherapy-only arms</td>
<td>50</td>
</tr>
<tr>
<td>Chemotherapy plus MoAb arms</td>
<td>15</td>
</tr>
<tr>
<td>5-FU/oxaliplatin-based trial arms</td>
<td>32</td>
</tr>
<tr>
<td>5-FU/irinotecan-based trial arms</td>
<td>26</td>
</tr>
<tr>
<td>5-FU/oxaliplatin/irinotecan arms</td>
<td>2 (FOLFOXIRI)</td>
</tr>
<tr>
<td>5-FU/other chemotherapy agents arms</td>
<td>1 (capecitabine + Mytomicin C + bevacizumab)</td>
</tr>
<tr>
<td>5-FU/biological agents only arms</td>
<td>2 (fluorouracil + folic acid + bevacizumab; capecitabine + bevacizumab)</td>
</tr>
<tr>
<td>Irinotecan/oxaliplatin (without 5-FU) arms</td>
<td>2 (irinotecan + oxaliplatin)</td>
</tr>
<tr>
<td>Bevacizumab-based arms</td>
<td>11</td>
</tr>
<tr>
<td>Cetuximab- or panitumumab-based arms</td>
<td>4</td>
</tr>
</tbody>
</table>

MoAb, monoclonal antibody; 5-FU, 5-fluorouracil; FOLFOXIRI, 5-fluorouracil + folinic acid + oxaliplatin + irinotecan.
43%, respectively. The difference between \( r \) coefficients (PPS and PFS) is statistically significant (\( P = 0.0005 \)).

The association between median OS and median PPS in recent trials (\( R^2 = 0.83 \) and \( r = 0.90, P < 0.0001 \)) was stronger than that in trials older than 2005 (\( R^2 = 0.52 \) and \( r = 0.75, P < 0.0001 \); Figure 3B and C), whereas the correlation between median OS and median PFS in recent trials (\( R^2 = 0.41 \) and \( r = 0.61, P < 0.0001 \)) was similar in older trials (\( R^2 = 0.52 \) and \( r = 0.54, P < 0.0001 \); Figure 2B and C). As well, the correlation between OS and PPS was \( r = 0.88 \) for arms that included a biological agent (bevacizumab, cetuximab or panitumumab); conversely, it was 0.59 between OS and PFS. In chemotherapy-only arms, the corresponding associations were 0.89 and 0.48, respectively (\( P \) for difference < 0.0001).

correlation between \( \Delta \text{PFS} \) and \( \Delta \text{OS} \) within trials

Among 34 trials, PFS was reported as an end point in 28 trials, TiP was reported in 5 trials and in 1 trial failure-free survival (instead PFS) was defined as the time from registration to the time of treatment discontinuation for any reason except death. So, this end point was deemed more similar to TiP. Overall, there was a good association between \( \Delta \text{PFS} \) and \( \Delta \text{OS} \) after inclusion of these 28 trials. The \( r \) value was 0.59 [95% confidence interval (CI) 0.28–0.78; \( P = 0.0007 \)] between \( \Delta \text{PFS} \) and \( \Delta \text{OS} \) (\( n = 29 \) arm comparisons). The results suggest that 1 month difference in PFS is associated with \( \sim 1.3 \) months difference in OS (slope 1.345; 95% CI 0.87–1.8; \( P = 0.000003 \)). These data also explain why the slope of PFS curve in Figure 2A is slightly more sharp than that in Figure 3A and confirms the biological value of the PFS measure.

discussion

In this paper, we investigated the relation between median OS and either median PPS or median PFS by the correlation analysis and found that overall median OS was, as expected, more strongly associated with median PPS than with median PFS, in particular in the period since 2005. The results highlights that, in recent years, correlation of OS with PPS becomes stronger than that of previous years (from \( r = 0.75 \) to \( r = 0.90 \), while in the same period of observation correlation of OS with PFS remain unchanged (from \( r = 0.54 \) to \( r = 0.61 \)). In particular, in arms including chemotherapy plus biological agents, the correlation PPS/OS was 0.88. However, our analysis confirmed that the improvements in PFS were strongly associated with improvements in OS in randomized, controlled trials of first-line chemotherapy for advanced CRC. Overall, these results confirm that PFS still represents a good surrogate end point over the years.

Tang et al. [5] carried out a similar analysis and found a greater correlation PFS/OS (\( r = 0.79 \)). They, however, did not split their analysis according to the publication period and included older trials (only nine trials included oxaliplatin or irinotecan schedules and only one trial a molecular targeted agent). Conversely, our analysis encompasses all trials with modern chemotherapies with or without approved targeted
therapies and confirms that PFS is still considered a good, surrogate end point.

The treatment of cancer patients is directed at prolonging their survival and/or giving them a better quality of life. Otherwise in the era of multiple lines of treatments, therapeutic options have been expanded in particular in CRC. In this situation, an OS benefit could be often diluted and masked by subsequent agents prescribed after progression of disease, and OS remains a not frequently meet end point in the first-line setting. In general, PFS should however be used cautiously as (surrogate) end point for regulatory approval of new drugs, in the era of new drugs [48].

In the present analysis, we defined median PPS as the median OS minus the median PFS for each treatment arm of phase III trials for the first-line treatment of patients with advanced CRC, as previously described by Broglio and Berry [9] in a breast cancer setting. Similar findings were recently presented by Buyse et al. [49] at 2012 ASCO Meeting. They found no influence of time of enrollment (before and after 2005), line of treatment (first versus second/third line) and type of trials (chemotherapy alone versus chemotherapy plus targeted agents) on ratio PPS/OS that is ~60%. Although our analysis was limited to chemotherapy doublets that are considered the standard, upfront treatment according to the clinical guidelines, the ratio PPS/OS is similar in the present analysis (56%).

In last decades, it is general concern that many factors other than more effective cure could have prolonged survival in trials of CRC patients: inclusion criteria in modern trials are more stringent [50, 51] and selection according to the biomarkers of response is planned, giving systemic treatment of CRC increasingly personalized and effective [52].

This strong association of PPS with OS is the result of the increasing number of active compounds, available also for second- or third-line chemotherapy in advanced CRC as discussed above. In the pivotal trial run by Hurwitz [11], ~50% of patients received second-line therapies, while in first-line cetuximab trial (CRYSTAL), two-thirds of patients received subsequent chemotherapy. PPS directly depends on the approval of these agents by health authorities for use in clinical practice through years but also on the rate of crossover to experimental drugs, the investigators decide to perform, after progression in control arms. In recent trials, the addition of an active agent as second-line therapy (e.g. irinotecan with or without cetuximab) or bevacizumab plus oxaliplatin after irinotecan failure led to median OS of 9.3, 10.7 and 12.9 months, respectively. These results were similar to those for PPS in recent trials (published after 2004) [53–55]. This confirms that active second-line (and beyond?) chemotherapy lines with or without biological agents led to a further survival gain. An increased rate of surgery of resectable metastases has been also implemented in recent years. About 12.5% of patients with unresectable liver metastases can be downstaged with modern chemotherapy and conducted to radical surgery according to Adam experience [56].

In 2009, Broglio demonstrated that for a trial with an observed P-value of 0.001 for improvement in PFS, there was a probability >90% of statistical significance in OS if median PPS was 2 months, but <20% if median PPS was 24 months. In our trials, PPS accounted for >50% of OS, and in recent trials, it is longer than 10 months compared with 8 months average median PFS in the same period. In first-line therapy, the availability of all active agents correlated with survival in the modern chemotherapy era [3]; however, these agents are today administered as part of a continuum of care through a strategy relying on a sequential line of agents. PFS more than objective response rate also correlates better with the final outcome in phase III trials, in particular when phase III studies include biological agents [57, 58]. These data, coupled with our finding that PPS in recent trials accounted for 83% of variation in OS compared with 52% in past trials, make survival a goal more difficult to meet for first-line trials, in particular when they include molecular agents. This confirms that with the advent of targeted therapies in particular, patients live longer and were more easily exposed to further lines of active therapies after failure of the first line.

In CRC, this is the first comprehensive analysis that correlates PPS and PFS with OS in trials published in the last decade including only targeted therapies. In particular, analysis of arms that included chemotherapy plus a MoAb shows that OS variation depends for 88% by PPS variation. However, the surrogacy of PFS with respect to OS was confirmed in our analysis and confirms the results of Tang et al. that analyzed even older studies.

In metastatic CRC, two different situations can be observed: (i) patients with resectable or borderline resectable (organ-confined) metastatic disease potentially amenable to cure and (ii) patients with unresectable disease where primary objectives of treatment are palliation and prolongation of survival. It seems appropriate, to consider in first situation as logical end points of modern, neoadjuvant, first-line trials (i) the response rate and (ii) the radical (R0) resection rate. Conversely, in phase III trials enrolling patients with unresectable and extensive metastatic disease, to explore the activity of new agents (palliative chemotherapy) could be acceptable to use PFS other than OS and quality of life as appropriate primary end points.

The present study has several limitations. First, our analysis included only literature-based data. The use of individual patient data might be expected to allow a better characterization of the relation between OS and other end points based on tumor assessment, including PFS or TiP. Secondly, the results of our study potentially have several confounders due to the selection of many heterogeneous trials for analysis. Thirdly, the assessment of disease progression is potentially subject to the measurement error and bias in individual patients, and the quality of measurement for end points based on tumor assessment can vary between centers and trials. Finally, these variations in PFS detection time could influence PPS estimates as recently showed in lung cancer [59].

Similarly, confounding effects of second- and third-line therapies other than inclusion criteria (fit and poor performance status patients mixed together) have been however observed commonly in solid tumors trials, which have led to a debate about the optimal end point of first-line trials [60]. Stage IV CRC has been transformed into a relatively chronic disease with median OS of ~2 years by new agents; thus, for ethical reasons, it is not possible to renounce to these active second or third lines, and adequate statistical adjustment
should be applied. So it is reasonable to consider PFS an acceptable end point for exploring the benefit of agents in first-line trials.

**conclusion**

Our findings indicate that, particularly for recent trials, PFS is highly correlated with OS in first-line trials in patients with advanced CRC, whereas PFS is only moderately associated. In particular, this association is corroborated in phase III trials exploring modern chemotherapy doublets plus a biological agents (either anti-VEGF or anti-EGFR MoAbs). In this case, PFS accounts for mostly of OS variation. We found also a good association between improvements in PFS and OS, so PFS continues to be a valid surrogate of OS.

It is necessary that a valid assessment of the clinical course after disease progression in every clinical trial, accounting for subsequent treatments, is implemented in future studies to better understand OS benefits. This could permit a statistically robust evaluation of survival with new drugs entering in clinical arena as upfront treatment of CRC.

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**disclosures**

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**references**


