Progression-free survival and time to progression as primary end points in advanced breast cancer: often used, sometimes loosely defined

E. D. Saad1* & A. Katz2

1Dendrix Research; 2Centro de Oncologia, Hospital Sírio-Libanês, Sao Paulo, Brazil

Received 4 September 2008; accepted 8 September 2008

Background: The growing availability of active agents makes the development of novel therapies increasingly complex and the choice of end points critical. We assessed the frequency of use of efficacy end points in advanced breast cancer.

Methods: We searched PubMed for randomized trials published between 2000 and 2007 in 10 leading medical journals. We abstracted data on progression-free survival (PFS), time to tumor progression (TTP), response rate (RR) and overall survival.

Results: A total of 58 studies enrolled 23 371 assessable patients in 122 treatment arms. The primary end points most frequently used were RR and TTP (n = 21 each), followed by PFS (n = 14). In five of the trials using TTP as the primary end point, no definition of TTP was reported; in 13 of the other 16 cases, death was counted as an event, making TTP indistinguishable from PFS. Trials having PFS, TTP or time to treatment failure as the primary end point (n = 36) had a higher mean number of patients than those using RR (P = 0.061).

Conclusion: Investigators seem to be frequently using PFS and TTP interchangeably in advanced breast cancer. Such use of terms may lead to confusion when results of different trials are compared, and uniform use of definitions seems in order.

Key words: breast neoplasms, disease-free survival, drug therapy, prognosis, survival analysis

Introduction

Over the past 15 years, significant advances have been achieved in the systemic treatment of advanced breast cancer. Foremost among these advances have been the introduction of novel chemotherapeutic agents [1], the use of aromatase inhibitors in postmenopausal women [2, 3], and of trastuzumab in patients with HER-2-overexpressing tumors [4, 5]. In addition, promising novel therapies in advanced breast cancer include the antiangiogenic mAb bevacizumab [6], the tyrosine-kinase inhibitor lapatinib [7], and the epothilone ixabepilone [8].

The growing availability of active agents against advanced breast cancer makes clinical development of novel therapies increasingly more complex. In addition to the growth in the number of possible drugs and combinations to be tested, and the possibility of testing novel therapies in different treatment lines, the choice of end points to be used in clinical trials is becoming a critical issue in drug development. Given its objectivity and the unquestionable benefit derived by patients, overall survival (OS) has been historically considered the most important end point in advanced breast cancer [9]. However, patient survival may be influenced by therapies used after participation in a given trial, and some randomized trials are actually underpowered to detect OS differences [10]. As a matter of fact, OS gain has only occasionally been achieved in the hundreds of randomized trials conducted to date in advanced breast cancer [9].

Progression-free survival (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 [11]. Many recent trials have used PFS or time to tumor progression (TTP) as the primary end points, with TTP theoretically differing from PFS in that the event of interest is only disease progression [12, 13]. Both PFS and TTP have traditionally been considered as surrogate end points for OS, as far as the drug approval process is concerned [14, 15]. Given the key role played by the choice of end points for clinical trials and for drug approval, we assessed the recent literature on advanced breast cancer regarding the use of efficacy end points in randomized trials, with the specific aim of quantifying the frequency of their use.
methods

search strategy and selection of the articles

To investigate the use of end points in clinical trials of advanced breast cancer, we searched PubMed using the medical subject headings ‘breast neoplasms’ and ‘drug therapy’, limiting the search to randomized controlled trials published between 1 January 2000 and 31 December 2007 in 1 of 10 leading medical journals in the field of cancer clinical trials (Annals of Oncology, Breast Cancer Research and Treatment, British Journal of Cancer, Cancer, European Journal of Cancer, Journal of Clinical Oncology, Journal of the National Cancer Institute, Lancet Oncology, The Lancet, and The New England Journal of Medicine). This search yielded 553 articles, which were then screened with the aim of selecting for analysis only those studies comparing two or more systemic antineoplastic therapies for advanced breast cancer. We excluded randomized phase II trials, studies on high-dose chemotherapy/bone marrow transplantation, combined result studies (i.e. papers reporting combined analyses of two or more separate trials), companion studies (e.g. on correlative biology or prognostic factors), and subsequent publications reporting additional results of trials already included in the articles selected for analysis. Also, two studies with factorial design were excluded from analysis because comparisons in such trials are not made between individual arms, thus precluding some of the analyses described herein [16, 17]. Except for six studies with three arms, all the other trials had two arms. Studies enrolling patients with locally advanced disease were included if the majority of patients had metastatic disease and if treatment had not been done in a neo-adjuvant fashion. When there was no mention of study phase in the title or abstract of the article, we included in the analysis only studies with >100 assessable patients in each arm and for which PFS, TTP, or OS was reported in the abstract. Such exclusions resulted in a total of 58 studies for the complete analysis (a list of these articles is available upon request). Such studies have been published in only eight of the target journals since no articles from the Journal of the National Cancer Institute or The Lancet fulfilled the selection criteria.

data abstraction and analysis

We abstracted from the full articles relevant data for analysis, with the goal of describing the extent to which the most important time-dependent efficacy end points (PFS, TTP, and OS), as well as response rate (RR), had been used in the recent literature. For each study, we obtained the primary and secondary efficacy end points following authors’ definitions in the paper; when the hierarchy of end points had not been clearly stated in the article, we ranked them in the order in which they were cited in the ‘Methods’ or ‘Results’ section of the paper. We also collected data on less common end points, such as duration of response, time to treatment failure (TTF), complete RR, and time to proven drug resistance [18]. The number of patients was the number of patients who were eligible for efficacy analyses, and the number of patients per arm was the latter divided by the number of arms (except for one study with a 2:1 randomization [19]). For studies in which the intent-to-treat (ITT) population was used for the primary analyses (or when the results of the ITT population were reported first, in the case of studies not specifying which was the primary analysis), the number of ITT patients was considered as the number of patients in the trial. We assessed the frequency and the consistence of the definition of PFS and TTP reported in the Methods or Results section of the articles. We abstracted the median follow-up for the PFS/TTP analyses when a separate follow-up was reported for the survival analyses. We also carried out exploratory analyses by comparing studies that were grouped according to specific characteristics. Means of normally distributed variables were compared with Student’s t-test, and the chi-square test was used for comparing proportions.

results

characteristics of the studies

Table 1 shows a summary of the main characteristics of the 58 studies included in the analysis. These studies enrolled a total of 23 371 assessable patients in 122 treatment arms. Approximately two-thirds of the studies included only patients with no prior therapy for metastatic disease. Thirty-six studies compared different chemotherapy regimens and included no hormone agents or targeted therapies; six studies had a targeted agent in at least one of the arms, regardless of the use of other drugs; 16 studies evaluated hormone therapies with or without chemotherapy. The median number of assessable patients per study was 329 (range 144–1354), and the median number of patients per arm was 157 (range 60–677). When reported, the median patient follow-up in these studies ranged from 11 to 72 months. Median follow-up was not available for 30 studies (52%).

use of end points in advanced breast cancer

As shown in Figure 1, the primary end points most frequently used were RR and TTP (n = 21 each), followed by PFS (n = 14), TTF, and OS (n = 1 each). RR was also the most common secondary end point overall (n = 31), followed by OS (n = 30), and duration of response (n = 25). When only the 39 first-line trials were considered (green bars in Figure 1), RR and TTP were again the most frequent primary end points (n = 14 each), followed by PFS (n = 9), OS, and TTF (n = 1 each). For the 39 trials published in the Journal of Clinical Oncology, TTF and RR were the most frequently used primary end points (n = 14 each), followed by PFS (n = 10), and TTF (n = 1). When chemotherapy-only trials were analyzed, RR was used in 16 cases, TTF in 10, PFS in nine, and OS was used once as a primary end point. Dividing the 58 trials according to the year of publication, 29 were published between 2000 and 2003

Table 1. Characteristics of randomized clinical trials in advanced breast cancer published between 2000 and 2003 in selected journals

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Journal of publication</td>
<td></td>
</tr>
<tr>
<td>Journal of Clinical Oncology</td>
<td>39</td>
</tr>
<tr>
<td>Annals of Oncology</td>
<td>5</td>
</tr>
<tr>
<td>Breast Cancer Research and Treatment</td>
<td>3</td>
</tr>
<tr>
<td>European Journal of Cancer</td>
<td>3</td>
</tr>
<tr>
<td>New England Journal of Medicine Cancer</td>
<td>2</td>
</tr>
<tr>
<td>British Journal of Cancer</td>
<td>2</td>
</tr>
<tr>
<td>Lancet Oncology</td>
<td>1</td>
</tr>
<tr>
<td>Treatment line</td>
<td></td>
</tr>
<tr>
<td>First only</td>
<td>39</td>
</tr>
<tr>
<td>First plus second ± third</td>
<td>12</td>
</tr>
<tr>
<td>Second ± third</td>
<td>7</td>
</tr>
<tr>
<td>Type of comparison</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy only</td>
<td>36</td>
</tr>
<tr>
<td>Hormone therapy ± chemotherapy</td>
<td>16</td>
</tr>
<tr>
<td>Targeted therapy ± chemotherapy</td>
<td>6</td>
</tr>
</tbody>
</table>
and 29 were published between 2004 and 2007. For the first period, RR was used as the primary end point 13 times, whereas RR was used 11 times during the second period.

**definitions of end points**

In five of the 21 trials using TTP as the primary end point, no definition of this end point was reported in the article. Analysis of the other 16 cases showed that progressive disease was always considered an event in TTP analysis. However, in 13 (81.3%) of these cases, death (either from breast cancer or from any cause) was also counted as an event. The definition of PFS was reported in the article in 13 of the 14 trials using this primary end point. In all cases, the events of interest in Kaplan–Meier analyses included both progressive disease and death. In the only study using TTF as the primary end point, TTF was defined as the time from randomization until progression, relapse, or death from any cause. Of note, only one trial used both PFS and TFP as efficacy end points; for this trial, the definition of TTP differed from that of PFS in considering only deaths from breast cancer, whereas PFS included death from any cause as an event.

**comparison between groups of studies**

Given the similarities between PFS, TTP, and TTF, and the fact that these end points have been used with equivalent intent in many trials, we grouped the studies that had one of these as the primary end points. We compared them with those using RR as the primary end point. As shown in Table 2, there were no significant differences between those two groups of trials in the parameters chosen for comparison. However, trials using RR as the primary end point had a smaller mean number of patients than trials that used PFS, TTP, or TTF ($P = 0.061$).

**discussion**

Our review of the literature suggests that PFS and TTP considered together are the primary end points most frequently used in randomized trials in advanced breast cancer. RR is another frequently used primary end point, whereas OS has been used in only 1 of 58 clinical trials. Our study also suggests that PFS and TTP have been used interchangeably by investigators.

The chief limitation of our study is the fact that we only looked at articles appearing within an 8-year period in one of eight selected medical journals, reasoning that these journals published most of the randomized clinical trials in advanced breast cancer. Although we have no reason to believe that such selection criteria have introduced bias in our analysis, it is conceivable that the assessment of articles published in other journals would lead to different conclusions, especially with regard to the frequency of use of primary end points and other quantitative issues relating to time-dependent end points. On the other hand, we believe our finding of the lack of consistency of the definition of TTP is noteworthy, independent of the adequacy with which the sample analyzed in our study is representative of randomized clinical trials in breast cancer in general. A second consideration regarding the limitations of our study is the fact that its design does not allow the assessment of publication bias. It is possible that negative studies, which would eventually stand a lower chance of being published, have used efficacy end points in different proportions than their positive counterparts. Also, the consistency of the definition of TTP may have been different in unpublished studies, when compared with published trials.

Methodological issues on end points have attracted considerable interest lately, especially in the fields of breast and colorectal cancer [13, 20, 21]. Members of the Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials (STEEP) group have pointed out that there is a lack of consistency in the definitions of many efficacy end points and that those definitions should be standardized to facilitate accurate communication among investigators, clinicians, regulatory agencies, funding agencies, clinicians, and patients, as well as exploratory cross-study comparisons [20]. The goal of that group is therefore to increase the quality of adjuvant breast cancer clinical trial conduct and reporting, while reducing the chances for miscommunication and misunderstanding on matters of interpretation of efficacy results from trials. That goal will hopefully be achieved through the proposal of specific definitions on end points to be used in clinical trials on the adjuvant treatment of breast cancer. Similar initiatives have been undertaken in colorectal cancer, both in the adjuvant [21] and in the metastatic disease settings [13]. To our knowledge, no similar proposals have been put forward to date regarding advanced breast cancer.

There has been a growing debate on the appropriateness of using OS as an end point in clinical trials in oncology. Such debate has been ongoing in the case of advanced colorectal cancer for several years [10, 12, 22, 23]. In colorectal cancer, OS...
Table 2. Comparison between randomized clinical trials in advanced breast cancer using different kinds of primary end point

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Primary end point</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, mean ± SD</td>
<td>PFS, TTP, or TTF (n = 36)</td>
<td>RR (n = 21)</td>
</tr>
<tr>
<td>Published in Journal of Clinical Oncology, %</td>
<td>448 ± 250</td>
<td>329 ± 178</td>
</tr>
<tr>
<td>First-line therapy only, %</td>
<td>69.4</td>
<td>66.6</td>
</tr>
<tr>
<td>Chemotherapy only, %</td>
<td>66.6</td>
<td>66.6</td>
</tr>
<tr>
<td>Published in 2000–2003, %</td>
<td>52.7</td>
<td>76.1</td>
</tr>
</tbody>
</table>

PFS, progression-free survival; TTP, time to tumor progression; TTF, time to treatment failure; RR, response rate; SD, standard deviation.

is considered by some as a flawed efficacy criterion since potentially active subsequent therapies are not controlled in many randomized trials, and measured OS may be increased or decreased by such therapies [22]. Evidently, the same reasoning may be applied in advanced breast cancer, given the existence of several effective lines of therapy [24] and the lack of control over treatments administered in subsequent lines. Although not looking specifically for this, we found only one study in our series in which second-line therapy was part of the protocol in all study arms [25]. Furthermore, in both advanced colorectal and breast cancer, many recently reported trials lacked power to detect a statistically significant increase in survival, even in the presence of other benefits [10].

Taken collectively, our study suggests that PFS and TTP have been used as primary end points in ~60% of recent randomized trials in advanced breast cancer. Both PFS and TTP have historically been considered as surrogate end points for OS, at least from the standpoint of drug approval [14, 15] and notwithstanding the controversy surrounding their formal validation in breast cancer [24, 26–28]. According to the Food and Drug Administration (FDA), PFS may be preferable to TTP as a correlate of OS because it is able to capture fatal toxicity in trials where the majority of deaths are expected to be related to cancer [29]. Perhaps the most notable finding from our study is the high frequency with which the definition of TTP included death as an event and not as reason for censuring. In some studies, the terms TTP and PFS have even been used interchangeably within the same trial [30, 31]. In the trial that used both PFS and TTP as efficacy end points, the definition of TTP considered only deaths from breast cancer, whereas that of PFS included death from any cause as an event [7].

TTF is usually defined as the time elapsed between treatment initiation and tumor progression, treatment discontinuation due to toxicity, patient preference, or death [11, 14]. A similar definition was used in some of the trials included in our review. However, in the only trial in our review using TTF as the primary end point, TTF was defined as the time from the date of randomization until the date of disease progression, relapse, or death from any cause without documented progression or relapse (i.e. a definition typically used for PFS) [32]. Such definition of TTF has also been used when this was a secondary end point [33]. Because TTF in its original definition is a composite end point that also includes symptom assessment, it is rarely accepted by the FDA in drug approval [14].

RR has been used as the primary efficacy end point in approximately one-third of the randomized trials included in our review. This is an interesting finding, given the known limitations of response assessment as an indicator of treatment benefit in oncology [34]. Exploratory analyses suggested that trials using RR as the primary end point tend to be smaller in size than those using PFS, TTP, and TTF. On the other hand, treatment type and setting, as well as journal and year of publication, did not appear to discriminate between these two main choices in end points.

In our study, we were surprised to find that the median follow-up was available for only 48% of trials, a proportion relatively similar to that reported recently by Mathoulin-Pelissier et al. [35], who found that the median follow-up was expressed in the results section for only 57% of 125 articles on various tumor types and treatment settings.

In conclusion, PFS and TTP seem to be the primary end points most frequently used in contemporary randomized trials in advanced breast cancer. However, PFS and TTP have often been used interchangeably. The lack of uniformity regarding the definition of end points may lead to miscommunication and to confusion when results of different trials are compared, and uniform adoption of the definitions seems therefore in order.

References