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Current Perspective

Clinical benefit in oncology trials: Is this a patient-centred or tumour-centred end-point?

*Pavlo Ohorodnyk, Elizabeth A. Eisenhauer, Christopher M. Booth**

NCIC Clinical Trials Group, Queen's University, Kingston, ON, Canada

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ABSTRACT

Background: Clinical benefit (CB) was first successfully used as an end-point in 1997 in the pivotal study of gemcitabine in advanced pancreas cancer. In the trial by Burris et al. CB was a composite measure of pain, performance status and weight. Here we describe how CB has been used in oncology trials since that time.

Methods: We performed an electronic search (www.jco.org) for reports of all clinical trials (phase I, II and III) published in the Journal of Clinical Oncology 1997–2008 citing 'clinical benefit'. Eligible trials were those reporting clinical benefit as an end-point. Details related to study methodology, sponsorship and end-points were abstracted. Use of CB was classified as patient centred if it referred to improvement in the clinical parameters used by Burris et al. or in other disease-related symptoms. CB was classified as tumour centred if it related to objective tumour criteria for partial/complete response and/or stable disease. Descriptive statistics were used to summarise findings and the chi-square test was used to compare proportions.

Results: Seventy-one trials reporting CB as an end-point were identified: 37 in breast, 8 in pancreas and 26 in other cancers. The definition of CB was patient centred in 20 trials (28%) and tumour centred in 51 trials (72%). Only 20% (14/71) of trials (including all 8 pancreas studies) used the original Burris definition. Among the 71 trials reporting clinical benefit, in only 31 (44%) cases was the end-point defined as a primary or secondary study objective. Trials with a patient-centred definition of CB were considerably more likely to do so than trials with a tumour-centred definition (19/20, 95% versus 12/51, 24%, $p < 0.0001$). Study variables associated with the use of a tumour-centred definition include: disease site (breast 35/37, 95%; all others 16/34, 47%, $p < 0.001$) and intervention (hormone or targeted agent 38/40, 95%; chemotherapy 13/31, 42%, $p < 0.001$). There has been a steady increase in the number of trials using CB as an end-point; in the second half of the study period the number of trials increased from 17 to 54, along with the proportion of trials with a tumour-centred definition (10/17, 59% to 41/54, 76%, $p = 0.09$).

Conclusions: Despite its initial definition, clinical benefit is often used to describe objective tumour findings. Clinical trials should use end-points in a consistent manner to enable clear communication between investigators, clinicians and patients about the benefit of novel therapies.

* *Corresponding author:* Address: NCIC Clinical Trials Group, Queen's University Cancer Research Institute, 10 Stuart Street, Kingston, ON, Canada K7L 3N6. Tel.: +1 (613) 533 6430; fax: +1 (613) 533 2411.
E-mail address: boothc@kgh.kari.net (C.M. Booth).

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1. Introduction

Most patients (and their oncologists) would define a useful therapy as one that increases survival and/or provides palliative benefit through improved quality of life (QOL). In the early clinical trials the observation of tumour regression may indicate biologic activity of a new treatment. Although subsequent study may find that this translates into improved survival or QOL, tumour response measurements in isolation are not synonymous with benefit to patients. While the past three decades have seen an encouraging reduction in the use of response rate as the primary end-point of randomised controlled trials; improvements in trial design and clarity in reporting trial results are still needed.[1,2]

'Clinical benefit' was introduced in the 1990s during the clinical development of gemcitabine for pancreas cancer[3] and was defined as a composite measure of pain, performance status and weight. In 1997 clinical benefit (CB) was successfully used as the primary end-point in the pivotal trial by Burris et al. which demonstrated that gemcitabine was associated with a substantial improvement in patient outcomes compared to 5-FU.[4] Despite only a minimal difference in survival, the improvement in clinical benefit changed the standard of care for this disease.

In the modern era of targeted therapy, clinical benefit is sometimes used to describe a decrease in tumour size or stable disease for a minimum period of time.[5] However, it can be argued that whether such patients experience true *clinical* benefit depends on whether they also have improvement in the duration and/or quality of survival. To explore our hypothesis that CB is frequently being used in a much different sense than it was originally defined by Burris et al., we reviewed the use and definitions of CB in oncology trials published since that time.

2. Use of 'clinical benefit' in oncology trials

We performed an electronic search (www.jco.org) for reports of all clinical trials (phase I, II and III) published in the *Journal of Clinical Oncology* (JCO) since the original Burris paper (June 1997–August 2008) citing 'clinical benefit'. Eligible trials were those presenting results for 'clinical benefit'. Details related to study methodology, sponsorship and end-points were captured. Use of CB was classified as patient centred if it referred to the improvement in the clinical parameters used by Burris et al.[4] or in other disease-related symptoms. CB was classified as tumour centred if it related to objective tumour criteria for partial/complete response and/or stable disease. Descriptive statistics were used to summarise findings and the chi-square test was used to compare proportions.

Since the pivotal trial by Burris et al.,[4] 71 trials published in JCO have included a clinical benefit end-point or described trial results using that terminology: 37 in breast, 8 in pancreas and 26 in other cancers (Table 1). The definition of CB was patient centred in 20 trials (28%) and tumour centred in 51 trials (72%). Only 20% (14/71) of trials (including all 8 pancreas studies) used the original Burris definition. The other 6 trials classified as patient centred used composite measures of other clinical end-points ($n = 5$) in isolation or in conjunction with tumour measurements ($n = 1$). Among the 71 trials reporting clinical benefit, in only 31 (44%) cases was the end-point defined as a primary or secondary study objective. Trials with a patient-centred definition of CB were considerably more likely to do so than trials with a tumour-centred definition (19/20, 95% versus 12/51, 24%, $p < 0.0001$).

Study variables associated with the use of a tumour-centred definition include: disease site (breast 35/37, 95%; all others 16/34, 47%, $p < 0.001$) and intervention (hormone or targeted agent 38/40, 95%; chemotherapy 13/31, 42%, $p < 0.001$). There was no association with sponsorship (industry 41/56, 73%; non-industry 10/15, 67%, $p = 0.86$) or phase of trial (phase I/II 36/48, 75%; phase III 15/23, 65%, $p = 0.56$). There has been a steady increase in the number of trials using CB as

Table 1 – Oncology trials reporting clinical benefit published in the Journal of Clinical Oncology 1997–2008.

	Patient-centred[a] end-point ($n = 20$)	Tumour-centred[a] end-point ($n = 51$)
Disease site		
Breast	2	35
Pancreas	8	0
Colorectal	3	2
Non-small cell lung	3	2
Renal	0	3
Other sites	4	9
Phase of study		
I	0	6
II	10	27
I–II	2	3
III	8	15
Sponsorship[b]		
Government	5	12
Industry	15	41
Foundation	1	5
Co-operative group	1	0
Not stated	4	2
Terminology used[b]		
Clinical benefit	12	28
Clinical benefit response	11	2
Clinical benefit rate	0	31
Intervention[c]		
Chemotherapy only	18	13
Targeted agent/hormone	2	38

a CB was classified as patient centred if it referred to improvement in the clinical parameters used by Burris et al.[4] or in other disease-related symptoms. CB was classified as tumour centred if it related to objective tumour criteria for partial/complete response and/or stable disease.

b Figures add up to more than 71 due to multiple sources of study funding and some trials using more than one terminology to describe clinical benefit.

c Trials without any molecular targeted or hormonal therapy were classified as chemotherapy only. If there was a targeted and/or hormonal agent involved in at least one study arm, the trial was classified as targeted agent/hormone.

an end-point; in the second half of the study period the number of trials increased from 17 to 54, along with the proportion of trials with a tumour-centred definition (10/17, 59% to 41/54, 76%, $p = 0.09$).

There was a considerable heterogeneity in the definition of CB among the 51 trials with a tumour-centred end-point. In 45 articles stable disease was used in combination with complete and/or partial response; in three further studies stable disease was used alone. Furthermore, there was little consistency in the duration of stable disease needed to qualify for CB in these trials. Among the 48 trials in which SD was a component of CB, the majority required stable disease to last for a minimum of 6 months ($n = 33$). However, we noted a considerable variation with duration criteria ranging from 3 months (4 trials) to 9 months (1 article). Duration of SD was not defined in 9 articles.

Terminology used to describe clinical benefit was also unclear. '*Clinical benefit response*' was predominately, but not exclusively, used to indicate CB as defined by Burris.[4] Of the 13 trials using '*clinical benefit response*', 9 used the Burris definition, 2 used other patient-centred definitions and 2 studies used the phrase in reference to objective tumour response. '*Clinical benefit rate*' was used exclusively by studies with a tumour-centred definition ($n = 31$).

3. Does this end-point benefit patients, clinicians or investigators?

Despite the initial patient-centred definition of clinical benefit as an end-point in oncology trials,[4] we have found that the majority of trials now using this term do so in reference to objective reduction or stability of measured tumour size. We have also found that the use of CB as a tumour-centred end-point is rarely pre-specified as a trial primary or secondary objective. Studies on breast cancer and trials involving a targeted agent or hormonal therapy are most likely to use a tumour-centred definition of clinical benefit. Furthermore, our data demonstrate very little consistency in definition of CB, particularly as it relates to duration of stable disease.

Clear and consistent language is essential for communication of research findings to investigators, clinicians and patients. Within oncology there are multiple examples of outcome definitions becoming standardised in an effort to improve communication and science. Widely used examples of standardised definitions include Common Toxicity Criteria established by the National Cancer Institute[6] and the Response Evaluation Criteria in Solid Tumours (RECISTs).[7,8] While tumour response rates and surrogates of survival such as progression-free or disease-free survival may provide evidence of biological activity, in only a handful of clinical conditions have these end-points been shown to correlate with improved quantity or quality of life for patients.[9–11] Our data demonstrate that clinical benefit as an endpoint is not clearly defined. Furthermore it is being used in reference to widely divergent assessments of both patient-reported outcomes and imaging-based tumour measurements. In their phase II trial of gemcitabine and capecitabine in patients with advanced biliary tract cancer, Koeberle et al. found that clinical benefit response (using the original Burris definition) did correlate well with formal quality of life measurements and to some degree with objective measurements of tumour response.[12] However, this example serves as the exception rather than the rule. Among the 51 articles in our review which define clinical benefit as a tumour-centred end-point, we did not find any examples where study authors demonstrated that tumour response criteria correlated with patient-reported outcomes or survival.

The importance of clarity in communicating the true benefit of cancer therapies is gathering increasing recognition.[1,2,13] At the same time, clinical investigators are developing new end-points in early phase clinical trials.[8,14,15] Inherent to the term clinical benefit is an understanding that patients will benefit clinically with the use of therapy. In oncology, like other fields of medicine, patients can benefit in one of two ways from treatment: they can live longer, or they can live better. Expectation of clinical benefit can potentially affect decision making in both practice and research. For these reasons we propose that the use of clinical benefit to refer to objective tumour measurements is not only inconsistent with its original definition, but is also frankly misleading to clinicians, patients and other investigators. Furthermore, the combined end-point of partial response, complete response and stable disease is already referred to widely in the literature as disease control rate.[16,17] We suggest that disease control rate is a more appropriate term for this combined end-point as it more accurately describes what is being observed clinically and is therefore less prone to misinterpretation.

In summary we have found that despite its initial definition, clinical benefit is often used to describe objective tumour findings. Clinical trials should use end-points in a consistent manner to enable clear communication between investigators, clinicians and patients about the benefit of novel therapies.

Conflict of interest statement

None declared.

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