REVIEW

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Best supportive care in clinical trials: review of the inconsistency in control arm design

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Background: Best supportive care (BSC) as a control arm in clinical trials is poorly defined. We conducted a review to evaluate clinical trials' concordance with published, consensus-based framework for BSC delivery in trials.

Methods: A consensus-based Delphi panel previously identified four key domains of BSC delivery in trials: multidisciplinary care; supportive care documentation; symptom assessment; and symptom management. We reviewed trials including BSC control arms from 2002 to 2014 to assess concordance to BSC standards and to selected items from the CONSORT 2010 guidelines.

Results: Of 408 articles retrieved, we retained 18 after applying exclusion criteria. Overall, trials conformed to the CONSORT guidelines better than the BSC standards (28% *vs* 16%). One-third of articles offered a detailed description of BSC, 61% reported regular symptom assessment, and 44% reported using validated symptom assessment measures. One-third reported symptom assessment at identical intervals in both arms. None documented evidence-based symptom management. No studies reported educating patients about symptom management or goals of therapy. No studies reported offering access to palliative care specialists.

Conclusions: Reporting of BSC in trials is incomplete, resulting in uncertain internal and external validity. Such studies risk systematically over-estimating the net clinical effect of the comparator arms.

Randomized controlled trials (RCTs) for patients with advanced cancer often use a best supportive care (BSC) control arm, whereby patients randomized to this control arm receive supportive care exclusive of anti-neoplastic treatment (Macdonald, 1998; Cullen, 2001; Ahmed *et al*, 2004; Zafar *et al*, 2008; Cherny *et al*, 2009). However, supportive care interventions provided to patients in BSC control arms are often poorly described in protocols and manuscripts (Cullen, 2001; Cherny *et al*, 2009; Zafar *et al*, 2012). A prior systematic review found poor reporting of the components of the BSC arm and a lack of BSC standardization among trial participants (Cherny *et al*, 2009). As a result of this lack of rigor in defining and standardizing BSC, studies including BSC control arms may have problems with internal and external validity (Figure 1). These validity concerns may lead to biased outcomes or flawed conclusions.

A panel of international experts developed consensus-based standards for delivering BSC in clinical trials (Zafar *et al*, 2012). The authors of this framework described four key domains that should be included in BSC delivery: (1) multidisciplinary care; (2) documentation of supportive care; (3) symptom assessment at least as often as the intervention arm; and (4) guideline-based symptom management (Zafar *et al*, 2012). Thus, this framework is intended to guide standardization of BSC in clinical trials similar to the way other frameworks improve consistency of RCTs and their reporting. For example, study interventions are described with great detail in the protocol; the CONSORT statement outlines

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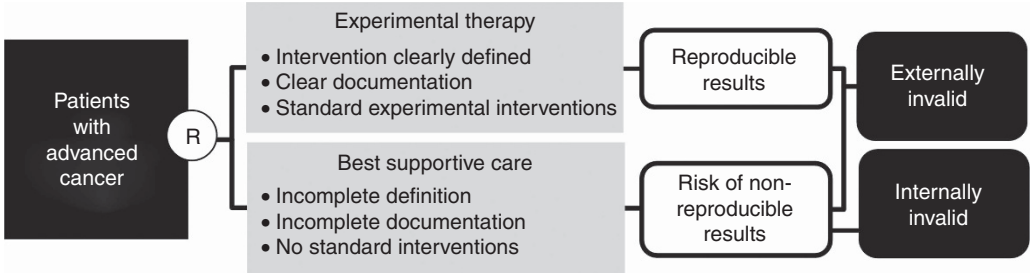

Figure 1. Poorly designed BSC can produce trial results that are internally and externally invalid.

Table 1. BSC and CONSORT domains assessed

BSC domains
Did the trial enroll patients across more than one site?
If yes, was the delivery of BSC standardized across all sites?
Was the delivery of supportive care within the clinical trial documented in a standardized manner for all patients on trial?
Does publication resulting from the trial offer a clear description of what best supportive care entailed?
Were symptoms are assessed at baseline and at regular intervals throughout trial participation?
Were symptoms assessed with concise, globally-accessible, validated tools?
Was symptom assessment undertaken at identical intervals in both arms?
Was symptom management conducted in concordance with evidence-based guidelines?
Were patients offered education specific to symptom management and assessment?
Were patients offered education specific to the goals of anti-cancer therapy?
Were patients offered access to palliative care specialists?
Did patients have access to other support services, including high-quality nursing, social work, financial counseling, and spiritual counseling?
Were patients educated on the goals of anti-cancer therapy, the importance of symptom assessment, and the role of symptom management within a clinical trial?
CONSORT domains
Does the study state eligibility criteria for patients?
Does the study document the settings and locations where the data were collected?
Are the interventions for each group described with sufficient details to allow replication, including how and when they were actually administered?
Does the trial provide adequate information for the results to be generalizable?

Abbreviation: BSC = best supportive care.

a consistent approach for documentation and reporting of patient eligibility criteria, study settings, intervention components, and generalizability of the trial findings (Schulz *et al*, 2010).

Although accepted standards for the delivery of BSC in RCTs exist, the literature has not described how well these standards reflect contemporary trial design. We conducted a review of the literature to determine whether the consensus-based framework for BSC delivery in RCTs reflects the design and documentation of recently published BSC RCTs.

MATERIALS AND METHODS

We searched the MEDLINE/PubMed database from 2002 to 2014 using the following search strings: 'cancer'; 'best supportive care'; 'randomized' or 'random allocation'; and 'supportive' or 'palliative.' We used the following exclusion criteria: no BSC arm, non-human trial, not randomized, not English, not advanced cancer, or not including anti-cancer therapy.

We assessed each article for conformance to the consensus-based guidelines for BSC delivery by determining the presence or absence of the guideline criteria in the study publication (Table 1). Similarly, we evaluated each RCT's concordance to selected methodological items derived from the updated CONSORT 2010 guidelines for the reporting of RCTs. We selected relevant items from the CONSORT 2010 guidelines that most closely resemble the BSC domains. Two reviewers evaluated each article to determine how well the consensus-based frameworks were reflected in the documentation of BSC in each trial. Two additional reviewers resolved any discrepancies to ensure consensus agreement on each particular guideline.

RESULTS

Search results. Of the 408 articles retrieved for potential review, we retained 18 after applying exclusion criteria (Figure 2). Most of the trials involved gastrointestinal (39%; 7 out of 18) and lung (39%; 7 out of 18) malignancies and most were phase III trials (78%; 14 out of 18) (Table 2). The majority of trials used overall survival as their primary endpoint (72%; 13 out of 18) and most concluded that their intervention showed an advantage over BSC (56%; 10 out of 18).

Conformance to BSC Delphi standards. Overall, trials conformed to 16% of the BSC Delphi standards. Although most of the studies were multisite trials (94%), none of them reported standardized BSC across study sites (Table 3). Only one of the studies reported standardized delivery of BSC for the participants assigned to this arm (6%). The authors of this study discussed standardizing supportive care in their methods section under the intervention subheading (O'Brien *et al*, 2006).

Two-thirds of the articles did not provide a clear description of what BSC entailed for the patients on the BSC arm. For example, a common description of care provided in the BSC arm included details about the patients receiving structured physical, psychological, and social assessments with a clear explanation of symptom management (Muers *et al*, 2008). Most of the articles described symptom assessment at regular intervals (61%), but fewer reported the assessment of symptoms at identical intervals for both arms (33%), or used validated symptom assessment tools (44%). None of the articles described the use of evidence-based symptom management and none of the articles mentioned the provision of education to patients regarding how symptoms would be managed. Similarly, we found that none of the articles discussed educating patients about the importance of symptom assessment and management.

Furthermore, none of the articles reported offering education specific to the goals of the trial and the anti-cancer therapy.

Table 2. Articles with BSC control arm

	Study	Disease	Treatment added to SC	Phase of trial	Line of Therapy	Total no. of patients	No. who received intervention	No. who received BSC	Primary End Point	Outcome	Conformance to BSC	Conformance to CONSORT
1	Thuss-Patience *et al*, 2011	Gastric	Irinotecan	III	Second	40	21	19	Survival	Advantage	17%	25%
2	Pelzer *et al*, 2011	Pancreas	Oxaliplatin, folinic acid and 5-FU	III	Second	46	23	23	Survival	Advantage	25%	25%
3	Machiels *et al*, 2011	H and N squamous	Zalutumumab	III	Second	286	191	95	Survival	No Advantage	0%	25%
4	Sharma *et al*, 2010	Gallbladder	Fluorouracil or gemcitabine plus oxaliplatin	Does not state	Not specified	81	54	27	Survival	Advantage	0%	50%
5	Harousseau *et al*, 2009	Acute Myeloid Leukemia	Tipifarnib	III	First	457	228	229	Survival	No Advantage	0%	25%
6	Ciuleanu *et al*, 2009	Pancreas	Glufosfamide	III	Second	303	148	155	Survival	No Advantage	17%	25%
7	Bellmunt *et al*, 2009	Bladder	Vinflunine	III	Second	370	253	117	Survival	Advantage	25%	25%
8	Jassem *et al*, 2008	Malignant pleural mesothelioma	Pemetrexed	III	Second	243	123	120	Survival	No Advantage	33%	25%
9	Van Cutsem *et al*, 2007	Colorectal	Panitumumab	III	Third or fourth	463	231	232	Progression-free survival	Advantage	0%	25%
10	O'Brien *et al*, 2006	Small cell lung cancer	Topotecan	III	Second	141	71	70	Survival	Advantage	33%	25%
11	Brodowicz *et al*, 2006	Non-small cell lung cancer	Gemcitabine	III	Maintenance after first line	206	138	68	Time to progression	Advantage	17%	25%
12	Spiro *et al*, 2004	Non-small cell lung cancer	Cisplatin-based combination	Does not state	Not specified	725	364	361	Survival	Advantage	17%	25%
13	Muers *et al*, 2008	Malignant pleural mesothelioma	Mitomycin, vinblastine, and cisplatin (MVP) or vinorelbine	Does not state	First	409	273	136	Survival	No Advantage	25%	25%
14	Jonker *et al*, 2007	Colorectal	Cetuximab	III	Second and beyond	572	287	285	Survival	Advantage	33%	25%
15	Kang *et al*, 2012	Gastric	Docetaxel or irinotecan	III	Second or Third	202	133	69	Survival	Advantage	33%	50%
16	Mubarak *et al*, 2012	Non-small cell lung cancer	Pemetrexed	II	Maintenance after first line	55	28	27	Progression-free survival	No Advantage	8%	25%
17	Reichardt *et al*, 2012	Gastrointestinal stromal tumors	Nilotinib	III	Third and beyond	248	165	83	Progression-free survival	No Advantage	0%	25%
18	Buikhuisen *et al*, 2013	Malignant pleural or peritoneal mesothelioma	Thalidomide	III	Maintenance after first line	221	111	110	Time to progression	No Advantage	0%	25%

Abbreviations: BSC = best supportive care; SC = supportive care.

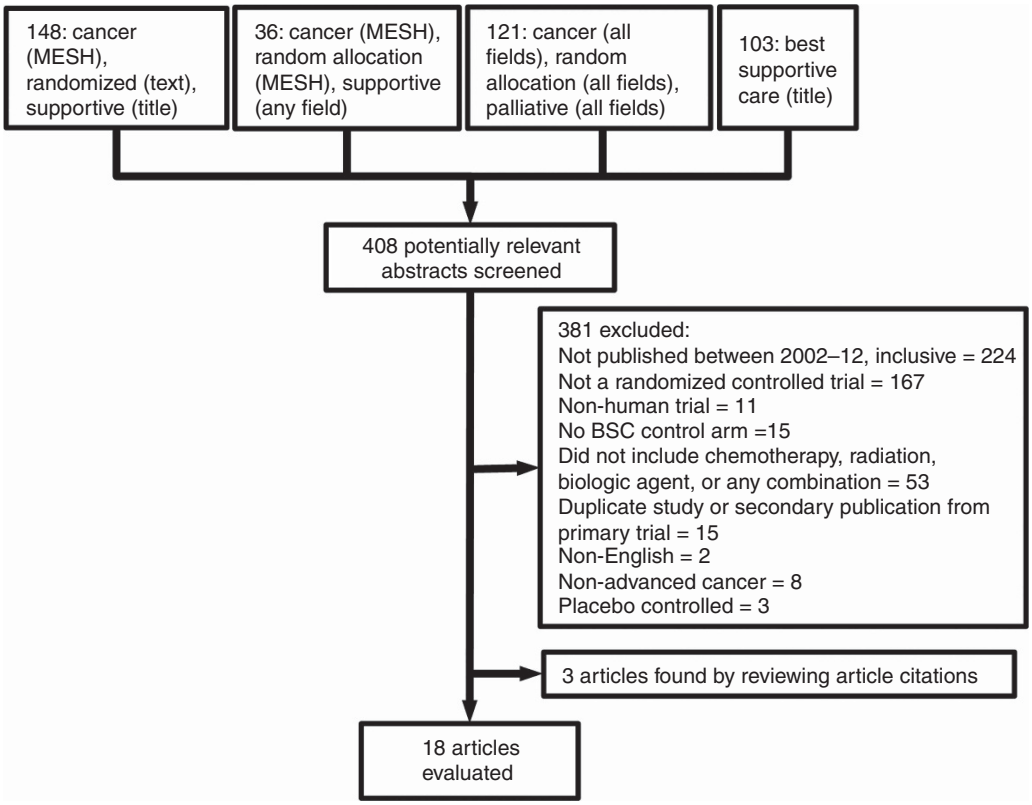

Figure 2. Literature review exclusion tree.

Table 3. Clinical trial conformance to BSC statements and CONSORT guidelines

Domain assessed	Yes
Conformance to BSC consensus standards in clinical trials	
Standardized BSC across sites if multisite	0%
BSC delivery standardized	6%
Clear description of BSC	33%
Symptom assessment at regular intervals	61%
Symptom assessment with valid tools	44%
Symptom assessment identical both arms	33%
Symptom management is evidence based	0%
Reported educating patients about symptom management	0%
Reported educating patients about goals of therapy	0%
Provided access to palliative specialists	0%
Provided access to support services	11%
Education about goals, importance of symptom assessment/ management	0%
Conformance to consort checklist for RCT's	
Eligibility criteria	100%
Documentation of settings	11%
Interventions described sufficiently	0%
Generalizable results (must have met all three of the above CONSORT criteria)	0%

Abbreviations: BSC = best supportive care; RCT = randomized controlled trial.

None of the articles mentioned that palliative care specialists were accessible to patients while receiving therapy. A minority of trials reported that patients in their study had access to support services that included social work, financial counseling, or spiritual counseling (11%).

Conformance to CONSORT. Overall, trials conformed to the selected CONSORT 2010 guidelines for trial reporting better than they did to the BSC standards (28% *vs* 16%). All of the articles reported eligibility criteria for patients on study. A minority of articles documented setting and locations of all trial sites (11%). None of the articles described interventions for each study arm with sufficient detail to allow replication. Similarly, none of the trials provided adequate information for the results to be generalizable.

DISCUSSION

In our review of the cancer clinical trial literature, we found inconsistent reporting of supportive care provided to trial participants. In contrast to efforts to standardize intervention arms, our findings are consistent with prior studies (Ahmed *et al*, 2004; Cherny *et al*, 2009) demonstrating that RCTs poorly define and standardize BSC as a clinical trial control arm. A systematic review published in 2004 sought to examine the outcomes of RCTs that compared BSC *vs* chemotherapy in gastrointestinal cancer clinical trials (Ahmed *et al*, 2004). This review concluded that trial design and reporting needed improvements, and it highlighted the need for more clearly defined BSC as an RCT control arm (Ahmed *et al*, 2004). Similarly, a 2009 systematic review of the BSC literature called for improvements to the methodological and ethical validity of BSC studies (Cherny *et al*, 2009). In response, consensus-based recommendations for BSC delivery were published in 2012 which sought to improve the internal and external validity of BSC trials for patients with advanced cancer (Zafar *et al*, 2012).

Using the recently published consensus-based framework for the delivery of BSC in clinical trials, we aimed to determine how well this framework reflects reporting standards for recently

published trials. Our current assessment of how well RCTs reflect these published BSC guidelines demonstrates potential avenues to improve the standardized delivery and documentation of supportive care in these trials. Most of the studies reported assessing patients' symptoms at regular intervals, but fewer reported using validated tools or standardizing these assessments across both arms. Furthermore, none of the articles discussed educating patients about the importance of symptom management, nor did they mention providing symptom management according to evidence-based standards. This lack of facilitation to access BSC, and poor standardization of symptom assessment and management in BSC trials merits attention, as BSC trials should deliver consistent, standardized supportive care according to published guidelines and evidence-based practice.

Standardization of supportive and palliative care in BSC trials is particularly important, as recent studies have found that patients with advanced cancer who receive palliative care experience improved quality of life, mood, and possibly even survival (Bakitas *et al*, 2009; Temel *et al*, 2010; El-Jawahri *et al*, 2011; Zimmermann *et al*, 2014). Access to palliative care should be provided early in the course of illness for patients with advanced cancer (Smith *et al*, 2012), especially those assigned to BSC in a clinical trial. The American Society of Clinical Oncology (Ferris *et al*, 2009) and the European Society of Medical Oncology (Cherny *et al*, 2003) both recommend the appropriate provision of supportive and palliative care services to patients with cancer. Our review of the BSC literature found that none of the recent trials document that patients had access to palliative care specialists. Additionally, these trials rarely report that patients had access to other support services, including nursing, social work, financial and spiritual counseling. Given that studies continue to show the benefits of providing optimal supportive care, BSC trials must aim to deliver care that complies with these accepted standards.

When BSC trials do not deliver standardized supportive care, researchers risk systematically over-estimating the net clinical effect of the comparator arms. This threat to internal validity calls into question the conclusions derived from the data. Notably, over half of the studies we analyzed found an advantage for the intervention arm compared with the BSC arm, but the use of substandard control arms may have inflated the effect sizes of the interventions. Furthermore, inconsistent reporting of the interventions received by the BSC control arm generates irreproducible data. Trial results that do not generalize to routine clinical practice lack external validity. Thus, in order for BSC trials to prove clinically meaningful results, researchers must provide consistent, evidence-based, and standardized BSC to all trial participants.

We recognize that all of the studies reviewed were published between 2002 and 2014. Thus, the study protocols were mostly written and implemented prior to the publication of the BSC Delphi recommendations. Hence, this current review serves as a 'line in the sand' documenting the current state and heralding an opportunity for improvement. Monitoring uptake of the standardized BSC framework over time will be illustrative, as perhaps the impact of the consensus recommendations will reverberate more with future BSC studies.

Proper trial design does not allow for poorly defined interventions and variation between sites. Consequently, our results show that studies complied with the selected CONSORT guidelines better than they did with the BSC consensus guidelines. Previously, a literature review of oncology trial compliance to the CONSORT checklist has shown that compliance improved over time, with the most recently published studies showing better reporting (Rodrigues *et al*, 2011). Although the included articles in our current review were reported after the publication of the BSC consensus statements, we did not specifically aim to track compliance with those standards. Rather, we aimed to determine how well those standards reflected contemporary clinical trial design. Therefore, just as compliance to the CONSORT checklist has improved over time, we hope compliance to the published BSC standards will improve in future BSC trials. Meanwhile, researchers, review boards, medical editors, and their peer reviewers should ensure that BSC trials adhere to accepted BSC standards.

In conclusion, inconsistent reporting of supportive care in BSC trials persists. In light of the recently published BSC consensus guidelines, our literature review highlights the need to improve the standardized delivery and documentation of supportive care in BSC trials. Patients with advanced cancer enrolled on clinical trials expect care based on the best available evidence, but too often BSC studies fail to standardize BSC delivery across trial sites, lack evidence-based symptom management, and do not provide access to palliative or supportive care services. These problems with trial design threaten internal and external validity, resulting in biased outcomes and potentially flawed conclusions. Researchers can overcome these threats by integrating the published BSC standards into their BSC RCTs, and improving their subsequent documentation of the components of their BSC control arm. Future efforts to improve BSC trial design will need to determine the feasibility of implementing the current BSC standards, and continue to adapt subsequent recommendations according to the standard of care and in concordance with the best available evidence.

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