Best Supportive Care: A Euphemism for No Care or a Standard of Good Care?

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This article seeks to address the question: Is best supportive care (BSC) in research a euphemism for no care or a standard of good care? The data regarding the ethical and methodological validity of BSC studies are reviewed. Most of the BSC studies published over the past 25 years are really treatment versus no treatment studies represented as BSC studies. By ignoring the best contemporaneous standards of BSC, standardizing practices in multicenter studies, validating participating centers, or documenting treatment delivery, researchers belie the stated intention of studying BSC. Most studies sought to evaluate if there was any benefit of a new anti-tumor treatment versus discontinuation of anti-tumor therapies. Overwhelmingly, and with few exceptions, the impact of BSC practices was not really part of the key research question. To be ethical and methodologically valid, BSC studies must incorporate standards consistent with contemporaneous, proven BSC practice standards. Work is underway to develop widely validated standards of practice for the control arm of best supportive care studies. These can be readily incorporated in to study development and evaluation.

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Since the mid 1980s best supportive care (BSC) studies have emerged as the dominant research paradigm for randomized controlled trials of new anticancer treatments for diseases hitherto unresponsive to treatment. The studies aim to identify therapies that improve the duration of survival or the quality of life over the current standard of care, which is the provision of palliative care. They emerged as an alternative to treatment versus no treatment studies, which had hitherto been the dominant research paradigm to address this issue.

BSC studies are heterogeneous and have involved two different designs: incorporating supportive care (SC) as a control arm (treatment v SC) or as a component of both arms (treatment + SC v SC alone). Since the early 1980s more than 30 of these studies have been published, most commonly in non-small cell lung, pancreatic, and gastrointestinal cancers. These studies—published in high impact journals, subjected to systematic reviews for specific diseases—are widely cited. They have contributed to substantial changes in practice, policy, and the funding of specific therapies.

The clinical value and scientific validity of this research approach has been criticized. It has been claimed that the SC in these studies is inadequately described, not consistent with any validated standard, routine rather than best, substandard, and delivered by physicians who were possibly inadequately skilled for the task.

WHY IS A ROUTINE PRACTICE STANDARD PROBLEMATIC FOR BSC STUDIES?

There is substantial evidence to indicate that routine SC often features inadequate evaluation of pain, failure to appreciate the presence and/or severity of symptoms, lack of consultation with experts in pain or palliative care, substandard pain treatment, and a lack of attention to psychological or existential distress or to family support. Furthermore, oncologists frequently feel inadequately prepared for this aspect of their work. In the United States, evidence to this effect was summarized in a report by the Institute of Medicine.

One of the obligations in clinical research is to minimize risk and maximize benefit to participants in research. One of the ways this is done is to ensure that the control arm of a randomized study is consistent...
with best contemporaneous clinical standards. In 2002 when the Helsinki Declaration was revised, a proposal to allow routine care as a standard for the control arm in clinical studies was dismissed and the best practice standard re-endorsed.

**2008 SYSTEMATIC REVIEW OF BSC STUDIES**

In a systematic review of studies published between 1966 and 2008, 43 papers were identified describing 32 studies. The studies were classified according to their study design: (1) treatment + SC versus SC alone (20 studies) or (2) treatment versus SC (12 studies). Based on a detailed review of the studies the authors concluded that, overwhelmingly, they were not compliant with Helsinki Declarations and not methodologically sound.

The most striking findings of the systematic review were that the researchers failed to review the contemporaneous standards for SC. Overwhelmingly the SC arm was described in minimal detail. With only three exceptions, no recognized practice standards for the SC elements were invoked. Even when invoked, they were infrequently elucidated and little evidence was presented to demonstrate the degree to which they were adhered to. No study incorporated justification for deviation from a best care standard. Eighteen used the superlative “best” to describe the SC (ie, “BSC”) without any justifying evidentiary qualification. This point is further illustrated by the manner in which SC was elaborated, typically listing therapeutic approaches such as palliative radiotherapy, analgesia, symptomatic care, and psychological care, rather than standards for assessment, implementation or monitoring. Only one study explicitly included more than one of the 10 recommended elements of SC derived from the 1990 World Health Organization (WHO) standards (Table 1).

These deficiencies pose major problems for the ethical and methodological validity of individual studies and this genre of research. The studies were noncompliant with at least two critical requirements of the Helsinki Declaration: first, that studies be predicated on a “thorough knowledge of the scientific literature,” and second, since 1975 the Helsinki Declaration has included a standard of care requirement for the control arm of randomized studies; from 1975–2008 the requirement was for a “best current care” standard, and since 2008, “best current proven care.”

Applying Consolidated Standards of Reporting Trials (CONSORT) criteria were applied to the methodological issues in complex nonpharmacological interventions like SC. The study found near universal noncompliance with methodological precautions to reduce bias. The commonly deficient methodological precautions included the following: careful description of the care providers and the centers in which participants were treated, eligibility of the care providers, including professional qualifications, expertise, or specific pretrial training (item 3); detail of the treatment components that may influence the outcome effect, including provision for individual subject condition, tolerance, and clinical course (item 4a); how interventions were standardized across centers (item 4b); assessment of protocol adherence (item 4c); and acknowledgment that results may be biased by the standards of care actually provided (item 20).

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<th>Table 1. Derived Standards for Best Supportive Care (BSC) Relevant to BSC Clinical Studies</th>
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<td>1. Adequate staff training for primary level providers of supportive and palliative care including oncologist and oncology nurses to ensure appropriate knowledge skills and attitudes in supportive and palliative care</td>
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<td>2. Interdisciplinary care with a minimum team of physician, nurse, and social worker</td>
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<td>3. Care coordinated to minimize the burden on patient, their caregiver(s), and family</td>
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<td>4. Routine patient evaluation using validated tools to evaluate the prevalence and severity of physical and psychological symptoms and the adequacy of social supports</td>
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<td>5. Treatment of physical symptoms, including pain, with evidence-based approaches and validated care pathways</td>
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<td>6. Patient monitoring for the adequacy of relief, and adjustment of treatment strategies as necessary</td>
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<td>7. Access to specialist palliative or pain management care for patients and situations that exceed the capabilities of the primary level care providers</td>
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<td>9. Availability of psychological and spiritual care for patients and their family members</td>
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<td>10. Ongoing care planning based on ongoing assessment, determined by goals set with patient and family, and with consideration of the changing benefit/burden of any treatment strategy</td>
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Furthermore, the authors pointed out that the methodological validity of the 12 studies that ostensibly randomized patients between anticancer treatment and SC were particularly problematic. The design implies that patients would receive one treatment or the other, and that this would serve as the basis for comparison between approaches. Given the symptom burden in advanced cancer and the clinical and ethical imperative to relieve distress, a clean comparison is implausible. Indeed, none of these studies specifically stated that symptom control was precluded from patients on the treatment arm and only five studies specifically described the provision of symptom control to patients on the treatment arm.34,36,56–58 It is unlikely that any patients in these nine studies were actually denied SC if it was needed.

Emanuel’s seven universally applicable requirements that provide a coherent and systematic framework for addressing ethical validity (Table 2)59 were applied. The review identified compliance issues with four of the seven requirements: social value, scientific validity, balancing of risks and benefits, and respect for enrolled participants. Lack of standards applied to the SC delivery of this body of research may have contributed to social harm. Rather than conveying the message that palliative and supportive care should be in accordance with best practice, this body of research implies that ad hoc routine care, bereft of any recognized standards, is a reasonable and acceptable standard. By not incorporating best contemporaneous SC practices the researchers did not meet their obligations to minimize risk or optimize benefits or display respect for potential and enrolled participants.

**Table 2. Seven Universal Criteria for Ethical Research**

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<th>Criteria</th>
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<td>1 Social value</td>
<td>Will this research derive knowledge or promote ends that will improve health, well-being?</td>
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<td>2 Scientific validity</td>
<td>Does the research apply valid methodology to generate reliable valuable data?</td>
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<td>3 Fair subject selection</td>
<td>No targeting of vulnerable for risky research or favor for potentially beneficial research</td>
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<td>4 Favorable risk-benefit ratio</td>
<td>Minimization of risks, enhancement of potential benefits</td>
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<tr>
<td>5 Independent review</td>
<td>By appropriately staffed IRB</td>
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<td>6 Informed consent</td>
<td>Informing participants of risk benefit and alternatives.</td>
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<tr>
<td>7 Respect for potential and enrolled participants</td>
<td>Permitting withdrawal, confidentiality, informing subjects of discovered benefits or risks, maintaining the welfare of participants</td>
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**HOW DID THIS HAPPEN?**

It may be that most of these researchers were genuinely unaware of standards of practice for supportive or palliative care. By self-report, a major proportion of oncologists receive inadequate training in this area.19–22 With only two apparent exceptions,24,28 it seems these studies were conducted without participation of clinicians with specific expertise in palliative care. Naiveté aside, the researchers can be fairly criticized for failing to carefully review the standards for supportive and palliative care contemporaneous with their investigations or to involve experts in the collaborative research process.60 Most leave the impression that they were treatment versus nontreatment studies represented as BSC studies but with no real effort to implement or evaluate best practices in SC. This raises the possibility of, at best, obfuscation and at worst deliberate deception. This applies to both the institutional review boards (IRBs) and the participants as to the true nature of the studies. IRBs clearly overlooked many of the ethical and methodological shortcomings. This may reflect a lack of familiarity with issues specific to the SC of advanced cancer, exaggerated evaluation of the researchers’ expertise in SC, or a lack of familiarity with the more complex methodological validity requirements of studies involving nonpharmacologic interventions.

When research is combined with clinical care, regulations, like the Good Clinical Practice (GCP) standards,65 provide inadequate protection for research participants. In advanced cancer in particular, current GCP standards are insufficient to ensure that patients will receive quality supportive and palliative care. Although most editors ostensibly insist on Helsinki and
GCP compliance and adherence to CONSORT criteria, in practice they have limited mechanisms to do so. More often than not IRB approval and informed consent are surrogates for Helsinki compliance, and judgments of methodological validity are left to peer reviewers who may or may not be familiar with the criteria to evaluate study validity.62

ARE THERE STANDARDS FOR BEST PRACTICES IN SUPPORTIVE CARE?

Standards for best current SC have existed in various formulations for more than three decades. The volume and quality of these formulations have developed in number and sophistication. The first of many textbooks to formalize this body of knowledge was published in 1978.63 International standards for best practice in cancer pain64 and palliative care for advanced cancer65 were first published by WHO in 1986 and 1990, respectively. Multi-author comprehensive texts describing best practices have existed since 1993.66 The current guidelines were derived from an extensive evidence base67,68 and are widely covered in major palliative care69 and oncology texts,70 monographs,71–73 and evidence-based standards of practice.74–81

IMPROVING FUTURE BSC STUDIES

Based on the findings of this review, the authors made a number of recommendations:

1. Since appropriate control selection is critical to ethical and scientific validity, the process should incorporate systematic review of the relevant literature about palliative and supportive care, formal involvement of clinical experts in palliative and supportive care, and circulation of the protocol to solicit critical appraisal.60,82
2. Research with a supportive care control arm must use adequate contemporary standard of SC.74–81 Failure to do so is unethical, and introduces bias that may undermine research validity.
3. Researchers must be adequately credentialed in SC. Appropriate quality-control measures must ensure that SC is consistent with recognized standards.55
4. In multicenter studies, SC practices should be standardized between centers.55
5. Study designs that preclude palliative care to participants (such as treatment v. SC) are never ethical.83,84
6. A logistically simpler alternative study design should be considered. A study design that randomizes treatment versus no treatment (or placebo) and SC off-study to all participants85–90 limits researcher liability for many of the complex standardization and validity issues invoked by inclusion of SC in study arms.55,91 This still provides SC and addresses the central question as to whether there is added benefit to the new treatment.

This genre of clinical studies has been severely hampered by the absence of a clear definition as to what constitutes a valid standard of practice for the control arm of BSC studies. The team that undertook the systematic review is developing a consensus document. This will provide standards and operationalized direction for a BSC arm in clinical studies that incorporate evidence-based best practice standard to meet Helsinki requirements. This is being developed using a Delphi approach and involves 30 professionally diverse experts, including oncologists, palliative care providers, and clinical trialists. Thus far in the consensus process they have agreed on 11 standards in four domains: multidisciplinary care, symptom assessment, symptom management, and documentation. For researchers, the final document will outline the standards and provide direction as to how to operationalize them. For IRBs, journal editors, and reviewers there will be guidance as to how to assess compliance with these standards.

SUMMARY

Are BSC studies a euphemism for no care or a standard of good care? Most of the BSC studies published over the past 25 years are really treatment versus no treatment studies presented as BSC studies. They had taken no effort to research the best contemporaneous standards of BSC, standardize practices between centers in multicenter studies, validate participating centers, or document treatment delivery. It is clear that they had no intention of studying BSC. Most studies sought to evaluate if any benefit of a new antitumor treatment versus discontinuation of antitumor therapies. With few exceptions, the impact of BSC practices was not really part of the research question. To be ethical and methodologically valid, BSC studies must incorporate a BSC standard consistent with contemporaneous, proven best practice standards. A widely validated standard of practice for the control arm of BSC can be readily incorporated in study development and evaluation.

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