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How is best supportive care provided in clinical trials for patients with advanced cancer? A review of registered protocols of clinical trials

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ABSTRACT

Background In 2012, 11 standards describing best supportive care (BSC) in clinical trials in advanced cancer were defined through consensus statements. The consensus included 15 key components. Our objective was to analyze whether clinical trials that involved patients with advanced cancer and that included BSC in at least 1 arm met the standards and contained the key components.

Methods We reviewed clinical trials registered in ClinicalTrials.gov, the ISRCTN (International Standard Randomised Controlled Trial Number) registry, the EU Clinical Trials Register, and the International Clinical Trials Registry Platform for 2012–2018. We selected only phase III studies in patients with advanced cancer that included BSC in at least 1 arm. We describe the characteristics of the trials, together with the definition and components of BSC. We analyzed how the trials met the standards and adopted the key components of BSC.

Results Of 193 trials retrieved, only 64 met the inclusion criteria; 36 of those trials (56%) had no definition of BSC. Less than 7% of the trials included even 3 of the 8 BSC standards that were defined to be included in the design of trials. Furthermore, trials mentioned only 5 of the 15 key components that the consensus defined to be fundamental, with symptom management appearing in 22% of trials and the other 4 components appearing in less than 8%.

Summary Most clinical trials registered during 2012–2018 that involved patients with cancer and an arm with BSC did not define the BSC concept. Hence, the design of those trials does not meet the consensus recommendations.

Key Words Clinical trials, hospice care, neoplasms, symptom assessment, quality of life, comprehensive health care

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INTRODUCTION

"Best supportive care" (BSC) expresses the care and attention—generally symptomatic or palliative—that patients should receive when included in the control arm of clinical trials testing new anticancer therapies[1]. The presumption is that BSC guarantees a control arm whose participants are not undertreated—at least in terms of support and control of symptoms—compared with participants who receive the investigational oncologic treatment.

Although BSC is usually presented as a standardized set of criteria, past experience indicates that BSC is an imprecise concept that has rarely been defined in the methods of clinical trials and, if defined, varies from protocol to protocol[2]. Although some authors understand BSC as palliative care[3], BSC does not conform to that concept, because palliative care is care for patients whose disease no longer responds to curative treatments and whose life expectancy is relatively short[4]. That existing imprecision has both clinical and ethics implications in relation to the care that patients

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with advanced cancer should receive when participating in clinical trials[5].

To overcome those limitations, a consensus published in 2012 presented a tool to define BSC in clinical trials with patients who have advanced cancer. The consensus set out 11 standards grouped into 4 domains: multidisciplinary care, documentation, symptom assessment, and symptom management (Table I). It also integrated 15 practical criteria or key components about how to perform BSC, agreed upon in the first part of the Delphi process of the consensus. The degree of compliance of clinical trials with the articulated standards was low before publication of the consensus and differed greatly depending on the criterion. Although 61% of trials that included BSC performed symptom evaluation, none included guideline-based symptom control[7]. And because current publications result from clinical trials designed years before publication of the consensus, we decided to assess the effect of the consensus by analyzing the designs of clinical trials registered since its publication.

The objective of the present study was to determine compliance with the recommendations of the consensus in the protocols of randomized clinical trials specifically relating to patients with advanced cancer. We examined the protocols of randomized clinical trials that were registered after publication of the consensus in 2012 and that expressly included BSC (or a similar treatment) in at least 1 trial arm.

METHODS

We reviewed clinical trials registered from the date of publication of the consensus, 1 February 2012, to 31 July 2018 in four international registries:

- ClinicalTrials.gov (https://clinicaltrials.gov/, U.S. National Library of Medicine)
- ISRCTN registry (http://www.isrctn.com/)
- EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/ctr-search/search)
- International Clinical Trials Registry Platform (https://www.who.int/ictrp/en/, World Health Organization)

The search was adapted to the conditions of each registry. All registries were double-searched: first with the terms "cancer" and "best supportive care," and then with "cancer" and "best supportive treatment." A further search limited to phase III clinical trials involving patients with advanced cancer was conducted in all registries where such a search was an option. Only trials that effectively defined in their methods that patients in at least 1 arm were assigned to BSC or a similar treatment were accepted. In all cases, the extended trial protocol was extracted from the registry Web site. All registered studies were included regardless of whether the study was still ongoing or already completed. The data were recorded and analyzed in the SPSS software application (version 15.0.1: SPSS, Chicago, IL, U.S.A.).

The variables extracted included title, key number of the study, year of registration, type of tumour, presence of a BSC definition, components of BSC, BSC in 1 or more arms of the trial, use of placebo, and references about how to implement BSC within the study. We analyzed concordance between the consensus components of BSC[6] and the elements that integrated supportive care into clinical trial protocols. The concordance analysis was limited to the multidisciplinary care, symptom assessment, and symptom management domains of the consensus (Table I). The 3 criteria in the documentation domain were not analyzed because they related to issues that are beyond the trial protocol, such as the attitudes of institutional board reviewers and journal editors, or effective documentation of the delivery of supportive care within a trial.

The analysis of the protocols was carried out by two authors (MESG, ASR). If no consensus was reached on the profile or the characteristics of a trial, the opinion of another author (LAFP, MLdVR) was obtained.

Ethics approval and consent to participate were not required because the research method was a documentary analysis of publicly available material.

RESULTS

In ClinicalTrials.gov, an advanced search of "interventional studies (clinical trials)" and "phase 3" was possible. That search returned 67 trials: 62 common to the two main

TABLE I Consensus-based standards for best supportive care in clinical trials in advanced cancer[6]

Domain	Standards
Multidisciplinary care	• Patients should have access to palliative care specialists while receiving anticancer therapy. • Patients should have access to high-quality nursing, social work support, financial counselling, and spiritual counselling. • Cooperative groups and institutional review boards should encourage formalization of the process to educate patients, so that they understand the goals of anticancer therapy, the importance of symptom assessment, and the role of symptom management within a clinical trial.
Documentation	• Institutional review boards should review trial protocols for documentation of supportive care methods. • The delivery of supportive care should be documented in a standard way for all patients. • Journal editors should ask for a clear description in reports of trials of what best supportive care entailed.
Symptom assessment	• Symptoms should be assessed at baseline and regularly throughout trial participation. • Symptoms should be assessed with concise, globally accessible, validated tools. • The intervals between symptom assessments should be identical in the intervention and comparator groups.
Symptom management	• Symptom management should be conducted in concordance with evidence-based guidelines. • Clinical trial protocols should encourage guideline-based symptom management.

searches ("cancer" and "best supportive care," and "cancer" and "best supportive treatment"), 4 from "cancer" and "best supportive treatment" only, and 1 from "cancer" and "best supportive care" only. In the ISRCTN registry, the search retrieved 32 trials: 29 common to the two main searches, 2 from "cancer" and "best supportive treatment" only, and 1 from "cancer" and "best supportive care" only. A search of the EU Clinical Trials Register produced 31 trials: 27 common to the two main searches and 4 from "cancer" and "best supportive treatment" only. Finally, 63 trials were found in an advanced search of the International Clinical Trials Registry Platform limited to "phase 3," but with no date limits; all 63 trials were found using "cancer" and "best supportive care." Of the total 193 registered trials, 89 were excluded because they did not meet the inclusion criteria, and after duplicates had been ruled out, the analysis was limited to 64 clinical trial protocols (Figure 1).

Table II presents the general conditions of the 64 protocols. We found no trial whose protocol referred to the consensus published in 2012. In 36 of the protocols (56%), BSC was not defined, and its objectives, components, or references were not described. In the other 28 trials, BSC was presented according to what the protocol itself defined as its objectives (improve quality of life; alleviate symptoms; optimize comfort, activity, and social support of patients and relatives), as the practical components of BSC (for example, drugs, techniques, or interventions), or as the criteria for delivering BSC to the patients included in the trial.

In 7 trials (11%), the fact that BSC includes administration of antitumour drugs was excluded (palliative radiotherapy was allowed), but in 4 trials (6%), antineoplastic treatments were expressly allowed with or within BSC. In 28 trials (44%), BSC was used in the control arm together with placebo, and in 41 trials (64%), BSC was included in both arms of the study and was not limited to patients who did not receive the experimental therapy.

In 16 trials (25%), the treatments, interventions, and techniques that constitute the consensus definition of BSC were referenced. Globally, those components (Table III) could be divided into nonspecific symptom control (for example, pain, gastrointestinal symptoms), psychosocial interventions (for example, spiritual and social support), administration of drugs for symptom control (for example, analgesia, corticosteroids, antiemetics, antidiarrheals,

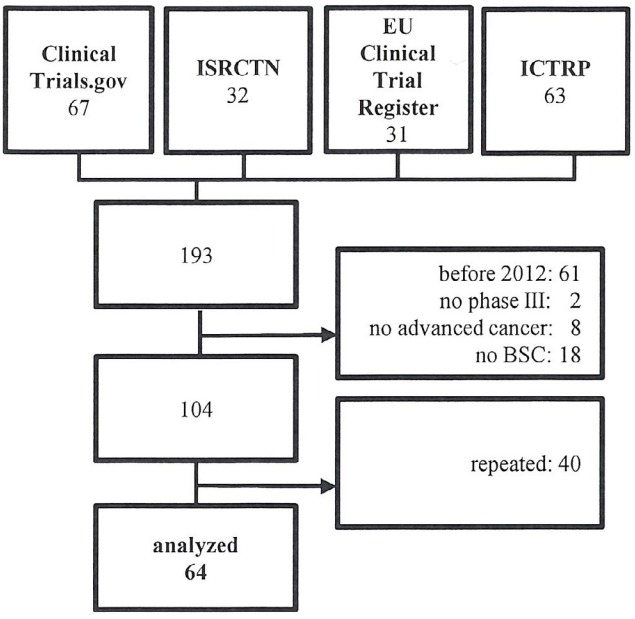

FIGURE 1 Flow diagram of the search for protocols in phase III clinical trials involving patients with advanced cancer. ISRCTN = International Standard Randomised Controlled Trial Number registry (now open to any study designed to assess the efficacy of health interventions in a human population); ICTRP = International Clinical Trials Registry Platform (of the World Health Organization); BSC = best supportive care.

TABLE II Characteristics of the protocols of the 64 randomized clinical trials involving patients with advanced cancer that were registered between February 2012 and July 2018 and that expressly included best supportive care (BSC) in at least one arm

Characteristic	Value	
	(n)	(%)
Year		
2012	7	11
2013	8	12
2014	7	11
2015	17	27
2016	14	22
2017	7	11
2018	4	6
Primary tumour		
Digestive	25	39
Lung	14	22
Urologic	9	14
Hematologic	7	11
Others	8	12
Pediatric (no primary specified)	1	2
Treatment or technique used in the study		
Chemotherapy	16	25
Monoclonal antibodies	14	22
Inhibitors (TKI, CDK4/6)	13	20
Experimental drugs or vaccines	8	13
Others	13	20
How BSC is explained in the trial protocol[a]		
No definition	36	56
Reference to concepts or techniques that integrate BSC	16	25
Reference to the objectives of BSC	4	6
Reference to who or what determines how BSC should be performed	14	22
How BSC is provided in the study[a]		
Provided in both arms of the trial	41	64
Expressly excludes anticancer treatment in the control arm	7	11
Expressly allows anticancer treatment in the control arm	5	8
Administered with a placebo	28	44

[a] Row items can total to more than 64 because the concepts might be not mutually exclusive.

TKI = tyrosine kinase inhibitor; CDK4/6 = cyclin-dependent kinase 4 and 6.

TABLE III Interventions included as best supportive care in clinical trial protocols

Intervention	Value	
	(n)	(%)
Analgesia	12	19
Antibiotics	9	14
Palliative radiotherapy	7	11
Transfusions	6	9
Nutrition support	5	8
Symptom control[a]	5	8
Blood products[b]	4	6
Corticosteroids	4	6
Correction of metabolic disorders	4	6
Antiemetics	3	5
Psychological support or psychotherapy[c]	3	5
Paracentesis	2	3
Palliative surgery	2	3
Referral to specialists in pain or palliative care, or both	2	3
Bone-protective agents	1	1
Antidiarrheals	1	1
Pleurodesis	1	1
Thoracentesis	1	1
Vitamins	1	1
Antipyretics	1	1
Oxygen	1	1
Appetite stimulants	1	1
Antidepressants	1	1
Spiritual support[c]	1	1
Social support[c]	1	1

[a] Including symptomatic gastrointestinal treatment.
[b] Erythropoietin, granulocyte colony–stimulating factor, and so on.
[c] Might be provided by a palliative care team.

antipyretics, appetite stimulants, or antidepressants), specific treatment of medical problems (for example, antibiotics, transfusions and blood products, nutrition support, treatment of metabolic disorders, bone-protective agents, vitamins, or oxygen), and techniques, even invasive, that could help to alleviate symptoms or other complications (for example, radiotherapy, palliative surgery, paracentesis, thoracentesis, or pleurodesis).

Of the 8 consensus standards analyzed, only 3 (37%) were included in a small proportion of the trials. Access to palliative care specialists was included in only 2 trials, access to multidisciplinary care was included in only 1 trial, and a reference to adopt evidence-based guidelines in symptom management was included in only 1 trial (Table IV).

Table V presents the 15 key components integrated into the consensus standards and indicates the number of clinical trials that included them. Of the 15 components, 10 (67%) defined in the consensus as key BSC components did not appear in any protocol, and the other 5 appeared in only a small proportion. Almost all the analyzed protocols excluded most key BSC components, including the need to evaluate and monitor symptoms, the use of validated instruments to measure symptoms, the process of discussing goals of care with the patient, and the integration of family.

DISCUSSION AND SUMMARY

A systematic search of clinical trials was not the objective of the present study. Even so, we accessed the most recommended[8] and highest-quality clinical trials registries, both international (International Clinical Trials Registry Platform) and specific to North America (ClinicalTrials.gov) and Europe (EU Clinical Trials Register, ISRCTN). It was not possible to access the metaRegister of Controlled Trials (http://www.isrctn.com/page/mrct) because that registry was under review at the time. We located 64 clinical trials that fulfilled the inclusion criteria, which allowed us to estimate the effect of the consensus recommendations.

Most of the analyzed trials included BSC in at least 1 arm, but did not define BSC or its objectives, treatments, and methods of application to patients. We understand that although BSC intends to improve quality of life and relieve symptoms by integrating various treatments and techniques (for example, pharmaceuticals, radiotherapy, transfusions), it is not an easy concept to define. In clinical trial protocols, BSC can be viewed as a combination of the palliation of symptoms associated with tumour progression and supportive management of the toxicities of chemotherapy or other antineoplastic drugs with antiemetics, transfusions, cytokines, or antibiotics. Formally, BSC does not exclude active cancer treatments, and in some trials (especially those treating patients with hematologic malignancies), cancer treatment and BSC seem to be integrated (see NCT02577406 at https://ClinicalTrials.gov/). In 1 trial, excluded from the study because it did not fulfil the inclusion criteria, BSC was combined with the least-aggressive cancer therapy (see 2009-016840-38 at https://www.clinicaltrialsregister.eu/ctr-search/search).

Our review of the evidence therefore suggests that the consensus definition has had almost no impact on the design of trials in advanced cancer that include BSC. On the one hand, there is no reference to the consensus, and on the other, there is a clear lack of compliance with the criteria and what the consensus lays out as the key components of supportive treatment in clinical trials[6] (Tables IV and V). Several trials defined medications, techniques, and interventions[9] (Table IV) that constitute BSC, but did not provide any indications about how those treatments would be given or how relevant symptoms should be assessed. Although most consensus participants preferred to define BSC as evidence-based supportive care[6], references to evidence-based guidelines in the analyzed trials are minimal. The common way to define how BSC should be performed within a trial is "usual practice" or physician or researcher preference. Only 1 trial set out standardized criteria (according to the recommendations of the World Health Organization), specifically with

respect to treatment of pain (see NCT01858571 at https://ClinicalTrials.gov/).

Publishing a list of criteria can be a praiseworthy initiative, but might be very inefficient. Hence, if the circumstances do not change, it is most unlikely that the consensus will have a greater impact in the future. A different, more practical approach would then be needed for researchers who design trials that include BSC.

How can clinical trial protocols maintain the relevance of the criteria presented in the consensus? It is evident that the proposed key principles of BSC (Table IV) resemble the principles of palliative care, including symptom assessment and management, multidisciplinary teamwork, a profile that integrates the psychological and spiritual, and integration of family[10]. Although none of the analyzed trials specifically addressed the recommendation that BSC should be provided by experts, it seems that the professionals who were more familiar with the principles of BSC were those integrated in a palliative care team[11], with experience in evidence-based early palliative care[12] for patients with advanced cancer receiving active anticancer therapy[13,14]. Hence, we must consider that oncologists and hematologists are more familiar with early palliative care[15]—provided by specific teams—than with the consensus recommendations[6]. Nowadays, the interdisciplinary palliative care teams treat patients with advanced cancer

TABLE IV Number of clinical trials that include the criteria of the consensus statement[6]

Statement	Value	
	(n)	(%)
Patients should have access to palliative care specialists while receiving anticancer therapy.	2	3
Patients should have access to high-quality nursing, social work support, financial counselling, and spiritual counselling[a].	1	2
Cooperative groups and institutional review boards should encourage formalization of the process to educate patients, so that they understand the goals of anticancer therapy, the importance of symptom assessment, and the role of symptom management within a clinical trial.	0	0
Symptoms should be assessed at baseline and regularly throughout trial participation.	0	0
Symptoms should be assessed with concise, globally accessible, validated tools.	0	0
The intervals between symptom assessments should be identical in both groups.	0	0
Symptom management should be conducted in concordance with evidence-based guidelines.	1	2
Clinical trial protocols should encourage guideline-based symptom management.	0	0

[a] The trial does not include all these options of interdisciplinary care.

TABLE V Number of trials that adopt the 15 key components of best supportive care in clinical trials[6]

Component	Value	
	(n)	**(%)**
Symptom management	14	22
Baseline symptom assessment with validated instruments	0	0
Follow-up symptom assessment with validated instruments, and treatment adjustment as needed	0	0
Intervals between symptom assessments identical to those for the investigational group	0	0
Use of standard, evidence-based symptom management guidelines	1	2
Documentation and reporting of supportive care assessment and delivery, including study protocols and reports	0	0
Access to palliative care specialists	2	3
Communication about care goals and care planning	0	0
Multidisciplinary care, including medical oncology, nursing, and social work	0	0
Family meetings and communication	0	0
Care coordination	0	0
Provision of psychosocial and spiritual care	1	2
Social support assessment	1	2
Instruction on self-care and education of patients	0	0
Financial resources assessment	0	0

receiving cancer therapy. If those teams were to be trained in the systematics of the trial's methods, especially in the evaluation and monitoring of symptoms, they could guarantee that all components of BSC would be provided.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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