Implementation of supportive care and best supportive care interventions in clinical trials enrolling patients with cancer†

R. T. Lee1*, K. Ramchandran2,‡, T. Sanft3 & J. Von Roenn4

1Department of Palliative, Rehabilitation, and Integrative Medicine, The University of Texas M. D. Anderson Cancer Center, Houston; 2Department of Medicine, Stanford University, Stanford; 3Department of Internal Medicine, Yale University, New Haven; 4Department of Medicine, Northwestern University, Chicago, USA

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Background: With the growing and evolving role of palliative care in oncology, we examined how supportive care (SC) and best supportive care (BSC) are implemented in clinical trials when used as a comparison treatment arm.

Methods: We conducted a systematic review of the literature for clinical trials published between 1980 and 2012 in which systemic anticancer therapy was compared with an SC-only arm and compared SC implementation with World Health Organization (WHO) published guidelines.

Results: Our search identified 189 articles, 73 of which met our inclusion criteria with the following cancer types: 29 lung, 7 colorectal, 6 pancreatic, 5 gastric and 26 others. Fifty-five studies (75%) provided some definition of SC, and 48 studies (66%) used the term BSC. Twenty-one of the 55 studies that provided a definition described the use of palliative therapies as being ‘at the discretion of the treating physician’ without standardization. Only two studies provided SC that incorporated routine physical, psychological and social assessments including rapid referral to SC specialists. SC interventions most commonly included analgesics (47%) and radiotherapy (44%). Trials using the term BSC versus SC were more likely to include blood transfusions (P = 0.002) and antibiotics (P = 0.033), but less likely to include steroids (P = 0.05) and palliative specialists (P = 0.047).

Conclusions: The implementation of SC in clinical trials in this systematic review is highly variable. The vast majority of the studies did not meet the WHO guidelines on SC because palliative care therapies were not recommended or integrated into care. Future clinical trials utilizing a SC intervention arm should define these interventions in a standardized approach that meets current guidelines such as the WHO recommendations.

Key words: supportive care, palliative care, best supportive care, cancer clinical trials

introduction

Beginning with Cecily Saunders in the 1960s, the field of palliative care was primarily focused on end-of-life care but has evolved to include care across the trajectory of disease [1]. Moreover, the field of palliative care has evolved to incorporate a variety of disciplines to provide a more comprehensive approach to patient care and is commonly referred to as palliative and/or supportive care. As defined by the World Health Organization (WHO), these therapies are aimed at improving the quality of life of patients and their families [2]. For the purpose of this study, we use the term ‘supportive care’ (SC) to encompass both supportive care and palliative care.

For patients with advanced/metastatic cancer, systemic chemotherapy is frequently the primary mode of treatment. The results of several reviews and meta-analyses have reported that chemotherapy provides a survival advantage over SC alone for patients with advanced cancer [3–7]. In some settings of advanced disease and/or poor performance status, the relative benefit of chemotherapy versus SC is unclear [8–10], and Cherny et al. have questioned the validity of this comparison [11]. Cherny’s publication highlighted significant ethical and methodological shortcomings among these studies in the context of CONSORT, the Declaration of Helsinki and the Universal Criteria for Ethical Research. Additionally, a study evaluating an early palliative care intervention for advanced lung cancer patients in combination with standard treatment compared with standard treatment alone demonstrated not only improved quality of life, but also an improvement in median survival [12]. However, the specific
components of the palliative care provided are incompletely defined, and few publications have quantified how SC is defined within clinical studies. Interestingly, the term ‘best supportive care’ (BSC) is commonly used, but without a clear indication of whether the clinical care interventions are considerably different or better than SC interventions. In other words, is BSC really describing best available care or maybe even no standard of care? [13].

We hypothesized that most clinical trials using the terms SC and BSC did not meticulously define what these interventions were or how they were delivered making the reported comparisons and conclusions invalid. This occurred in spite of the fact that several clinical guidelines have been established to help create standards for supportive and palliative care services for patients with cancer. Such guidelines are generally ‘informed by a systematic review of the evidence’ and ‘include recommendations intended to optimize clinical care’ [14]. One of the earliest definitions and clinical guidelines comes from the WHO. The WHO first published a report in 1990 on palliative care [15], and this was incorporated in the second edition of their National Cancer Control Programs: policies and Managerial Guidelines in 2002 [2]. The WHO publication provides definitions around components of SC and concepts on the provision of this care for cancer patients. Since this time, several other national and international organizations (e.g. ASCO, NCCN, NQF, NICE, etc.) [16–19] have been publishing guidelines regarding SC services for cancer patients and have been providing more information on actual clinical practice guidelines. Hui et al. [20] have highlighted the high degree of heterogeneity on how SC and similar terms are defined in published studies. Of note, this study found that the majority used the WHO definition of palliative care, and this recommends supportive interventions, within four core areas (physical, psychological, social and spiritual), to be provided in an integrated manner with support teams that address both patient and family needs [2]. To determine the actual degree of conformity in the implementation of SC in clinical cancer trials, we conducted a systematic review of the literature with three aims: (i) to explore how SC and BSC are defined in cancer clinical trials; (ii) to evaluate whether the term BSC is associated with different interventions and services as compared with SC; and (iii) to determine whether studies offering SC or BSC adhere to WHO guidelines.

methods

We performed a systematic review of the literature and identified clinical trials that compared a systemic anticancer therapy with SC. We queried three databases—Pubmed (Ovid), Embase (Ovid) and the Cochrane Central Register of Controlled Trials—to identify clinical trials with publication dates from 1980 to 2012 that met the following inclusion criteria: clinical trials that clearly stated (in either the title or the abstract) that SC composed a key intervention of at least one of the comparison treatment arms involving cancer patients versus a systemic anticancer treatment. The following combination of terms were accepted as equivalent to SC: (best or active) ± (‘supportive’ or ‘palliative’ or ‘symptomatic’) + (‘treatment’ or ‘care’ or ‘therapy’ or ‘control’ or ‘measures’) ± (‘only’ or ‘alone’). Publications were limited to clinical trials published in English. We excluded clinical trials that did not specifically include SC as a component of treatment. For example, treatment X versus placebo clinical trials, with no reference to SC, were excluded. We also excluded clinical trials that included SC followed by delayed systemic therapy or only an interventional therapy (e.g. palliative surgery or palliative stent) as a comparison arm. This literature search including search terms and topics was conducted by a medical oncologist (R.L.) with the guidance of a medical librarian and co-authors (T.S., K.R. and J.V. R.). The results were imported into EndNote X2 (The Thompson Corporation, Berkley, CA), and duplicate references were eliminated. The authors (R.L., T.S. and K.R.) independently reviewed all search results and together determined publications that met the criteria for study inclusion. Authors conducted aspects of snowballing methodology by checking the reference lists of relevant articles including published reviews of the topic. Any discrepancies identified were discussed and resolved with consensus (i.e. agreement among the three primary authors—R.L., T.S. and K.R.).

After determining which articles were relevant, the same authors independently extracted the following information: primary author; year clinical trial was published; year clinical trial started enrollment; the number of subjects enrolled and assigned to the SC arm; cancer type and stage; treatment plan; placebo use; whether SC was defined and if so, how was it defined in identified categories (analgesics, radiotherapy, steroids, antibiotics, nutritional consultation, blood transfusions, antiemetics, psychological consultation, psychiatric medications, social support, spiritual support, palliative specialist, others); whether the term BSC was used; the surveillance strategy and whether this strategy was equal in both treatment arms; difference in survival duration between study arms; and whether the utilization of SC services was reported for each group. In some instances, the date of initial enrollment was not provided and thus the publication date was substituted. The authors reviewed the collected data for agreement and analyzed the data to determine the definition of SC and whether the term BSC differed from SC.

We used the published WHO guidelines as the standard for SC because these guidelines were one of the first widely published reports on SC and is commonly cited in the literature [2, 20]. Additionally, this report provided more of a global perspective in contrast to other publications which might be viewed as country-specific since many of the clinical trials were conducted internationally. Descriptive analyses are reported as percentages of common categories of therapies included in definitions of SC. To examine whether differences in adherence to WHO guidelines existed over time, we grouped trials that started enrolling patients before 2003 and those that began enrolling thereafter. This time period was chosen because the second edition of the WHO cancer guidelines was published in 2002, which included a section on palliative care. We also grouped trials into those using the term BSC and those using SC (or a similar term, i.e. palliative care). To assess differences in survival, median survival duration (weeks) was calculated and compared between groups. Pearson’s chi-squared test was used to compare groups and a $P < 0.05$ was considered statistically significant. All data analyses were performed using STATA SE (Version 10; Thomson Co.; College Station TX).

results

The initial search identified 15 570 articles from the three databases. Removal of duplicates and review of the titles and
abstracts eliminated the majority of these publications, leaving 189 articles for analysis. We retrieved these articles and reviewed them for inclusion based on preset criteria. Seventy-three articles met the inclusion criteria (Figure 1). A list of the primary articles and general information regarding the identified articles are included in supplementary appendix 1, available at Annals of Oncology online [21–93]. These studies included 21,736 subjects, 6,986 of whom were assigned to a SC-only treatment arm. The most common cancer population studied was patients with nonsmall-cell lung cancer (38%), followed by colorectal cancer (10%), pancreatic cancer (8%) and gastric cancer (7%). A minority of studies involved a placebo (14%). All but one solid tumor clinical trial included stage IV patients or those with advanced disease, defined as refractory, recurrent or nonsurgical disease [88]. The median survival duration was 28.0 (SD 31.4) weeks in the systemic anticancer therapy arm and 20.4 (SD 26.7) weeks in the SC arm. The median difference in survival duration between the two study arms was 7.7 weeks (SD 10.1).

Thirty-four trials (47%) clearly reported that the clinical evaluation schedule was the same in the SC arm as in the treatment arm, while 16 studies (22%) had different evaluation schedules. The remaining studies (32%) did not provide adequate information to determine whether the evaluation schedules were equivalent. Documentation of specific SC therapies utilized during the study was reported only in 25% of the publications.

defining SC

Most of the studies (75%) provided a nonspecific definition of SC. Common definitions of SC included: ‘Supportive care was defined as the best care available as judged by the attending physician, according to institutional standards for each centre’ [34] or ‘Best palliative care was given at the discretion of the investigators, and included the option of palliative radiotherapy, opioid analgesics and psychosocial support’ [44]. SC defined as ‘at the discretion of the investigator’ was found in 29% of studies. Only a few studies provided a detailed definition of the SC intervention; for example, Cartei et al. included detailed information about the types of medications, their doses and the schedule recommended for symptom control [28]. Only two clinical trials (Muers et al.) employed a regular follow-up in a palliative care specialty clinic [61, 62].

Therapies that were included in the SC definitions were identified and then categorized (Table 1). Only one of the identified studies mentioned spiritual support for subjects, although no further details were described. Approximately a quarter of studies (22%) provided a definition of SC that included

<table>
<thead>
<tr>
<th>Category</th>
<th>All N (%)</th>
<th>SC N = 25</th>
<th>BSC N = 48</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics</td>
<td>34 (47%)</td>
<td>13 (52%)</td>
<td>21 (44%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>32 (44%)</td>
<td>13 (52%)</td>
<td>29 (40%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>20 (27%)</td>
<td>3 (12%)</td>
<td>17 (35%)</td>
<td>0.033</td>
</tr>
<tr>
<td>Steroids</td>
<td>19 (26%)</td>
<td>10 (40%)</td>
<td>9 (19%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Blood transfusions</td>
<td>19 (26%)</td>
<td>1 (4%)</td>
<td>18 (38%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Psychological support</td>
<td>13 (18%)</td>
<td>4 (16%)</td>
<td>9 (19%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Nutritional counseling</td>
<td>12 (16%)</td>
<td>2 (8%)</td>
<td>10 (21%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Social work</td>
<td>9 (12%)</td>
<td>4 (16%)</td>
<td>5 (10%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Antiemetics</td>
<td>8 (11%)</td>
<td>2 (8%)</td>
<td>6 (13%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Antidepressants/anxiolytics</td>
<td>4 (5%)</td>
<td>3 (12%)</td>
<td>1 (2%)</td>
<td>0.077</td>
</tr>
<tr>
<td>Palliative specialist</td>
<td>2 (3%)</td>
<td>2 (8%)</td>
<td>0</td>
<td>0.047</td>
</tr>
<tr>
<td>Spiritual support</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (2%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Other therapies (e.g. thoracentesis, pleurodesis)</td>
<td>12 (16%)</td>
<td>2 (8%)</td>
<td>10 (21%)</td>
<td>0.16</td>
</tr>
</tbody>
</table>
psychological and social support, most often described as ‘psychosocial support or care’ [40, 44, 50]. Among studies that provided a definition of SC, radiotherapy and analgesics were most commonly cited as components of the prescribed SC, present in over 40% of the identified studies. Palliative medicine specialists were rarely utilized (3%).

**BSC versus SC arm**

Approximately two-thirds (66%) of the studies specifically used the term BSC to describe the SC arm. Studies using the term SC defined the intervention in 80% of those trials, while studies using the term BSC defined the intervention 73% of the time. In the study defined provision of BSC versus SC, there was a higher likelihood of including blood transfusions (38% versus 4%; \( P = 0.002 \)) and antibiotics (35% versus 12%; \( P = 0.033 \)) as a component of supportive therapies in the BSC studies. However, studies using the term SC had a higher likelihood of including steroids (40% versus 19%; \( P = 0.05 \)) and a referral to a palliative care specialist (8% versus 0%; \( P = 0.07 \)) as compared with studies using the terms BSC. No statistical difference was seen in the prevalence of use of psychosocial health professionals (e.g. psychologists or social workers; see Table 1).

**differences in clinical trials beginning enrollment before and after 2003**

Approximately two-thirds of the studies (49) began recruiting patients before 2003. The use of the term BSC increased from 59% for studies enrolling before 2003 to 79% among studies enrolling subjects after 2003. Of the 24 cancer clinical trials that began enrolling subjects with cancer in 2003 or later, only 14 (58%) provided a definition of SC. This was significantly less than for studies enrolling subjects before 2003 (84%; \( P = 0.018 \)). For studies enrolling before 2003, SC was more likely to be comprised of analgesics (55% versus 29%; \( P = 0.037 \)), radiotherapy (59% versus 13%; \( P > 0.001 \)), steroids (37% versus 4%; \( P = 0.003 \)) and the use of other therapies (23% versus 4%; \( P = 0.048 \)) as a defined component of the SC intervention. Inclusion of psychosocial health professionals was also more frequent before 2003 than after 2003—psychological support (27% versus 4%; \( P = 0.023 \)) and social work (18% versus 0%; \( P = 0.048 \)). See Table 2.

**discussion**

Our retrospective review of more than 30 years of randomized clinical trials with a SC treatment arm demonstrates the lack of a consistent definition of SC in these trials and, as a result, highly variable management of subjects who were randomly assigned to the SC treatment arm. Surprisingly, studies using the term ‘best’ SC (BSC) and those that began enrolling patients after 2003 did not, as a whole, provide more clearly defined SC interventions for subjects who were randomly assigned to the SC treatment arm. Our results add additional support that the SC provided in clinical trials of patients with advanced cancer does not meet current published guidelines [11, 13, 94, 95]. Together with the results published by Temel et al., these findings should prompt further discussion regarding the value of systemic anti-cancer therapy in advanced cancer patients as some previous studies may have overestimated the benefits of the intervention when compared with SC. With a more standard approach to SC in future clinical trials assessing anti-cancer therapy versus SC, we may find that certain populations may not benefit from systemic chemotherapy and that SC may be the best option.

The field of palliative care advocates for a comprehensive approach that addresses all dimensions of health, and the published guidelines by WHO and other international organizations support this multidimensional approach. Indeed, the concept of a multidimensional model of healthcare has been present for many years such as the biopsychosocial model proposed by George Engel over 30 years ago [96]. Extensive research has demonstrated the high prevalence and significance of both psychological and social distress among cancer patients [97–100], and in the clinical trials identified in this study, it is unclear that the high burden of suffering experienced by this population was adequately addressed. A definition of SC, especially in the context of clinical trials, must include key elements of a multidimensional model (physical, psychological, social and spiritual) as described by WHO guidelines [2]. A recent review by Zafar et al. aimed to describe the available standards for SC delivery and guideline dissemination [94]. They concluded that while guidelines do exist in the form of ‘broad consensus statements’ and ‘published guidelines’, implementation or dissemination has been limited. This study supports these conclusions.

| Table 2. Comparison of therapies included in SC clinical trials before and after 2003 |
|-----------------------------------|-----------------|-----------------|-----------------|---------|
| Category                          | Before 2003 (N | After 2003 (N | P-value |
|                                   | %) N=49 | %) N=24          |           |
| Analgesics                        | 34 (47%) | 27 (55%) | 7 (29%) | 0.037 |
| Radiation therapy                 | 32 (44%) | 29 (59%) | 3 (13%) | <0.001 |
| Antibiotics                       | 20 (27%) | 14 (29%) | 6 (25%) | 0.75 |
| Steroids                          | 19 (26%) | 18 (37%) | 1 (4%) | 0.003 |
| Blood transfusions                | 19 (26%) | 11 (22%) | 8 (33%) | 0.32 |
| Nutritional counseling            | 12 (16%) | 10 (20%) | 2 (8%) | 0.19 |
| Psychological support             | 13 (18%) | 13 (27%) | 1 (4%) | 0.023 |
| Social work                       | 9 (12%) | 9 (18%) | 0 | 0.025 |
| Antiemetics                       | 8 (11%) | 7 (14%) | 1 (4%) | 0.19 |
| Antidepressants/antianxietytics    | 4 (5%) | 4 (8%) | 0 | 0.15 |
| Palliative specialist             | 2 (3%) | 2 (4%) | 0 | 0.32 |
| Spiritual support                 | 1 (1%) | 0 | 1 (4%) | 0.15 |
| Other therapies (e.g. thoracentesis, pleurodesis, etc.) | 12 (16%) | 11 (23%) | 1 (4%) | 0.048 |
Access to palliative care specialists has been shown to improve quality of life and symptom control for patients with advanced cancer [12, 101, 102]. Furthermore, the majority of the patients enrolled in the reviewed trials would have been eligible for hospice care, a source of excellent patient and family support for symptom control as well as other domains of distress [103, 104]. One potential solution is to incorporate routine, systematic assessments of patients’ symptom needs in all dimensions; thereby helping to identify which patients would benefit from a palliative care specialist evaluation [99, 105]. More recent guidelines from the National Consensus Project and National Quality Forum have emphasized the importance of structured approaches to the delivery of SC with clear processes to facilitate optimal SC interventions [18]. Another important effort underway is the incorporation of palliative care training for all oncology fellows, with some fellowship programs requiring several weeks to months of clinical rotations in palliative care or the option of combined training in oncology and palliative medicine.

A comprehensive SC approach should be considered an active intervention. Beyond symptom management and quality of life, some evidence indicates that psychosocial interventions may affect survival duration, although this finding has not been consistent across studies [106–109]. A survival benefit has been demonstrated from the addition of SC [12]. The term BSC should be used judiciously to avoid misleading potential subjects about the extent of therapeutic interventions provided. Early on, Cullen suggested that a more appropriate term would be ‘standard’ SC, a sentiment echoed by others [8, 9, 13]. This may be especially relevant since many clinical trials are now conducted within an international network where considerable differences exist in the standard of care, the terminology used to describe supportive and palliative care, and the available resources for cancer patients. Future clinical trials evaluating the benefit of any systemic anticancer therapy, with or without SC, must, at a minimum, meet the guidelines set forth by the WHO to be considered valid comparisons of the impact of an intervention on survival and quality of life. In practical terms, health-care providers with expertise in SC therapies must not only be available, but integrated into patient care systems such that physical, psychological, social and spiritual distress can be addressed adequately. Therefore, clinical trials must provide a clear definition of SC, adequate assessment of symptoms using validated instruments specific to the cancer type being treated (e.g. Functional Assessment of Cancer Therapy—Lung), use of palliative care specialists (or those with expertise and training in symptom management) within an integrated system of care, and detailed documentation of provided SC interventions. Zafar et al. convened a panel of experts, and used a modified Delphi method to develop a consensus framework for defining the delivery of BSC in clinical trials. Key components included a multidisciplinary care model, meticulous assessment and management of symptoms and appropriate documentation of BSC methods to allow for results to be reproduced in standard practice [110]. However, developing and implementing a universally accepted all-encompassing definition of BSC for cancer patients will be difficult because of the unique complexities of each cancer type, treatment, and population—for example, elderly cancer patients [111]. Understandably, a clinical trial conducted at a single institution will have a simpler task in implementing a standard SC approach than an international, multi-center clinical trial, especially when incorporating cultural differences in care.

Despite our extensive literature search methodology with the aid of a medical librarian trained in systematic reviews, some relevant clinical trials may not have been identified. Further efforts such as hand searching and sensitivity testing may have helped us to further minimize the risk of overlooked articles. The large heterogeneity between patient populations in these studies makes comparisons limited especially in regards to clinical outcomes. It is also possible, though unlikely that the protocols of the reviewed clinical trials may have provided a detailed description of SC interventions that were not presented in the published articles. An attempt was made to contact the study authors to address this; however, only a minority of requests resulted in further information being obtained.

summary

The findings of this retrospective review identify the absence of a standardized approach to interventions in clinical trials for patients with advanced cancer. BSC and standard SC have essentially no distinct difference in the collection of articles reviewed. Furthermore, none of the SC care plans provided by these clinical trials met WHO guidelines. A framework for considering a comprehensive approach to SC for cancer patients is provided by the WHO guidelines as well as several other international organizations on palliative care. These guidelines and a BSC definition for cancer must include assessment and treatment of physical, psychological, social and spiritual dimensions of suffering. Future clinical trials should adhere to specified guidelines, provide a uniform SC intervention that is fully integrated into patient care pathways, and collect relevant data on quality of life and SC therapies provided.

funding

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disclosure

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