Current Hematologic Malignancy Reports (2018) 13:155–163
https://doi.org/10.1007/s11899-018-0445-y

The Effect of Psychosocial Interventions on Outcomes for Caregivers of Hematopoietic Cell Transplant Patients

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Abstract

Purpose of Review Hematopoietic cell transplant (HCT) patients are required to have a caregiver present for up to 100 days post-transplant. Caregivers provide essential support during HCT but experience immense stress and burden. Increasing research has developed interventions for HCT caregivers. This review systematically evaluates psychosocial interventions for caregivers of HCT patients.

Recent Findings The search yielded 12 studies (7 efficacy and 5 feasibility studies) enrolling 931 caregivers. Interventions were feasible and acceptable as evidenced by high rates of completion (70–100%) with attrition due to patient morbidity or mortality. Feasibility was augmented by flexible delivery (in-person, teleconference, smartphones, or Web-based platforms). Acceptability was demonstrated by objective measures of satisfaction. Effectiveness was found for fatigue and mental health service use, but not for burden, sleep-quality, and inconsistently for caregiver depression, anxiety, coping, and quality of life.

Summary Psychosocial interventions are feasible, acceptable, and show mixed effects on HCT caregiver outcomes.

Keywords Family caregivers · Psychosocial intervention · Hematopoietic stem cell transplant

Introduction

Hematopoietic cell transplantation (HCT) is a costly and intensive cancer treatment used to treat multiple hematologic malignancies and some solid tumors. With the relative success of HCT, the prevalence of autologous (auto; self-donor) and allogenic (allo; alternative donor) HCT survivors in the USA is increasing and projected to reach over 500,000 by 2030 [1]. Most transplant centers deem the caregiver to be so critical in contributing to the effectiveness of HCT that they require HCT candidates to have a caregiver available for 24 h a day, for 30–100 days post-HCT. During the pre-HCT period and for months or years post-HCT, caregivers are the essential partners for reducing patient risks for rehospitalization, infections, and mortality [2–4]. The critical role of HCT caregivers has increased scientific and clinical attention to the psychosocial, physical, and financial impacts of caregiving. Research indicates that HCT caregivers report elevated levels of distress, anxiety, burden, uncertainty, as well as declines in physical health, fatigue, and quality of life [4–7]. Compared to HCT patients, caregivers report lower marital satisfaction post-transplant and experience similar emotional and greater social long-term costs of cancer [8, 9]. A small, but growing body of research has focused on developing psychosocial interventions for HCT caregivers. Interventions have typically focused on education, preparedness, coping, relationships, problem-solving strategies, self-care, and well-being [10]. Psychosocial caregiver interventions often provide training in appraisal of stressors and aim to enhance the educational and emotional resources of caregivers and optimize strategies used to moderate stress appraisals [11]. In this systematic

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This article is part of the Topical Collection on *Health Economics*

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11899-018-0445-y) contains supplementary material, which is available to authorized users.

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review, we assess the evidence of the feasibility and effectiveness of these interventions on caregiver outcomes. In cancer prevention and control, feasibility studies produce findings that help determine whether an intervention should be recommended for larger-scale testing, whereas intervention efficacy is defined as meeting intended behavioral outcomes under ideal circumstances [12]. We draw from the Transactional Model of Stress and Coping, which emphasizes that the degree to which care stressors impact caregivers' life are mediated by subjective appraisal of stressors, as well as resources for coping with stressors [11]. In this review, consider how caring for someone undergoing HCT may negatively affect caregiver outcomes, and how resources delivered through interventions may optimize caregiver well-being (Fig. 1). Our review addresses two key questions:

1. Are HCT caregiver interventions feasible and acceptable?
2. Are HCT caregiver interventions effective in optimizing caregiver outcomes?

Methods

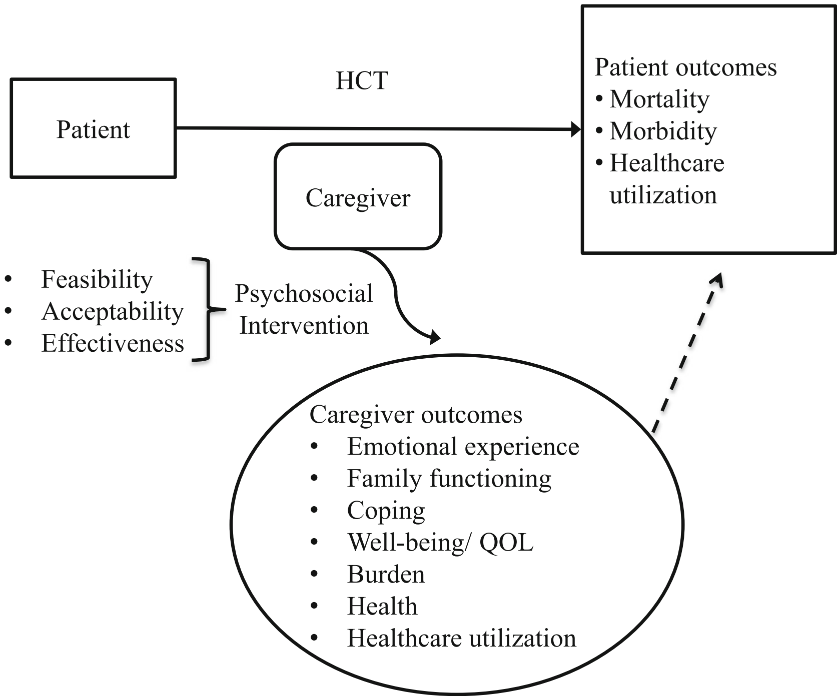
Search Methods

A comprehensive search of several databases from each database's inception to October 10, 2017, was conducted. Controlled vocabulary supplemented with keywords ("hematopoietic stem cell transplant" OR "hematopoietic cell transplant" OR "bone marrow transplant" AND "psychosocial intervention" OR "intervention" OR "programs" OR "services" AND "caregiver" OR "patient and caregiver" OR "patient" OR "survivor" Or "dyad" OR "dyadic") was used to search for psychosocial interventions for caregivers and patients in stem cell transplantation. The databases included Ovid Epub Ahead of Print, Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, and Ovid EMBASE, Ovid PsycINFO, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for psychosocial interventions for caregivers and patients in stem cell transplantation. The search strategy is available in the appendix.

Inclusion Criteria

Inclusion criteria included any study published in English with interventions that enrolled adult (≥ 18 years) caregivers of adult patients undergoing myeloablative and non-myeloablative allo- or auto-HCT. Interventions were required to include some level of caregiver involvement (e.g., patient-focused but caregiver-assisted, caregiver-focused, patient/caregiver dyad focused) *and* a quantitative assessment of a caregiver outcome. We included all study designs, including randomized controlled trials (RCTs), cohort studies, and

Fig. 1 Analytic framework psychosocial interventions for HCT caregivers



alternative designs. Exclusion criteria included descriptive or qualitative studies and studies with interventions that assessed only patient outcomes. Studies that did not report caregiver outcomes resulting from the intervention were excluded. Studies with caregivers of pediatric HCT patients were excluded due to differences in patient life stage, treatment, priorities, symptom management, and caregiver responsibilities.

Study Selection and Data Collection

Two independent reviewers completed the following steps. First, titles and abstracts were screened to assess eligibility for inclusion. The full-text publications were then retrieved and eligibility for inclusion was assessed. Data were abstracted from each study using a Microsoft Excel spreadsheet-based extraction form developed in accordance with the Cochrane Review Handbook [13]. The following data were abstracted: patient and caregiver descriptive data (inclusion criteria, age, sex, and stage of transplant when enrolled in the intervention) description of intervention and control (setting, design, duration, dropout rates, blinding, randomization, and replication) outcome measures, and results. The funding source for all studies was extracted. Incongruity between the two reviewers was resolved by meeting and establishing consensus.

Outcomes of Interest

The primary outcomes were indicators of caregiver well-being, including self-reported quality of life, mental health, affect, family adjustment, and subjective stress. Other outcomes were physiological/biological measures of stress.

Data Synthesis and Analysis

For key question 1 (*Are HCT caregiver interventions feasible and acceptable*?), data from feasibility and pilot studies were synthesized through narrative review. For key question 2 (*Are HCT caregiver interventions effective in optimizing caregiver outcomes*?), we constructed an evidence map to visually display and summarize the evidence from HCT caregiver interventions [14]. For RCTs and cohort studies, we evaluated the quality of the study using the Cochrane Risk of Bias tool and the Newcastle-Ottawa quality assessment scale for nonrandomized studies, respectively [15, 16]. For RCTs, we evaluated adequacy of randomization, allocation concealment, blinding (patients, caregivers, interventionists, and outcome assessors), baseline imbalance, and loss to follow-up. For nonrandomized cohort studies, we extracted representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and demonstration that the outcome of interest was not present at the start of study.

Results

A total of 186 references were identified through our search method. After abstract review, 160 did not meet inclusion criteria. The remaining 26 papers were reviewed and from that review, an additional 14 studies did not meet inclusion criteria because they were not interventions, did not include caregivers/caregiver outcomes, or were focused on pediatric HCT. Of the remaining 12 studies, 5 were intervention feasibility studies and 7 were intervention efficacy studies (4 RCTs and 3 cohort studies).

Description of Studies

Study details are available in Table 1. In general, caregivers were defined as an individual who assumed primary responsibility for care of HCT patients throughout the transplantation process. Common exclusion criteria included history of psychiatric illness or neurologic disorder, unable to speak or read English, being treated for an acute health problem, or under age 21.

Out of the 12 studies, the search identified 5 studies that focused on establishing preliminary acceptability or feasibility for an intervention. These feasibility studies included, in total, 250 caregivers (range 9 to 148). One dyadic feasibility study included patients, all others studied only caregivers. Caregivers in feasibility studies were mostly female (66%) with a mean age of 53 years. One study enrolled caregivers of patients receiving auto- or allo-HCT [19], one study enrolled caregivers of patients receiving only auto-HCT [21], and the remaining three studies enrolled caregivers of patients receiving only allo-HCT [17, 18•, 20].

We identified seven efficacy studies comprised of three cohort studies and four RCTs of moderate quality. Studies included a total of 681 caregivers (range 24 to148). Three studies included patients in the intervention. Participants were enrolled in interventions at different stages of transplant, ranging from pre-transplant hospitalization to post-transplant. Follow-up ranged from 3 weeks to ~ 3 months post-transplant. Caregivers in efficacy studies were mostly (67%) female with a mean age of 53.73 years. Two studies enrolled caregivers of patients receiving either allo- or auto-HCT [23, 24]. Four studies enrolled only caregivers of patients receiving allo-HCT [22, 25–27]. One study exclusively enrolled caregivers of patients receiving auto-HCT [28].

Risk of Bias Within Efficacy Trials

None of the studies provided details about allocation concealment, blinding of participants, and blinding of outcomes. Based on these criteria, all studies had moderate risk of bias (see supplementary tables). Our assessment of intervention quality must be interpreted within the context of psychosocial

Table 1 Characteristics and description of HCT caregiver interventions

Author (reference) Objective	Description of intervention	Patient population	Feasibility/acceptability	Challenges to feasibility/acceptability
Feasibility studies				
Pensak et al. [17] Objective: reduced perceived stress, anxiety, and depression.	Mobile website-9 session caregiver stress management intervention (mobile adaption of [18•]).	Auto	Intervention is acceptable; brevity and flexibility contributed to acceptability.	Intervention was dependent on internet access; usability of mobile device.
Heermann et al. [19] Objective: Optimize technical skill of caregivers in central-line care.	In-person class and modified objective structured clinical examination to build skills in central line care.	Allo and Auto	Intervention is feasible.	Intervention is labor intensive.
Metoyer [20] Objective: Provide preparation for the caregiver role.	In-person educational intervention program.	Allo	Intervention was beneficial and needed; most appropriate timing of is after discharge.	None discussed.
Bevans et al. [21] Objective: Optimize problem solving skills and distress.	In-person 4 session dyadic problem solving educational intervention.	Allo	Dyadic intervention is acceptable; intervention during scheduled hospital visit contributed to feasibility.	Patient symptom distress; caregiver time is limited; number of sessions; scheduling sessions.
Simoneau et al. [18•] Objective: Reduce caregiver distress.	In-person 8 session stress management intervention for caregivers including cognitive behavioral strategies, psychoeducation, and problem-solving skills.	Allo	Intervention is feasible; use of a biofeedback device is unacceptable by caregivers; sessions must be flexible.	Scheduling in-person sessions; caregiver time is limited; patient death or illness.
Author (reference) Objective	Description of intervention	Patient population	Sample	Stage of transplant/duration
Efficacy studies				
Bevans et al. [22] Objective: Improve self-efficacy and distress.	(Cohort) 3-session problem solving education sessions (efficacy study of [21])	Allo	Caregiver $n = 101$ Patient $n = 70$	Intervention began during eligibility screening and continued during the first 3 weeks of transition to outpatient care
El-Jawahri [23] Objective: Improve quality of life, depressive symptoms.	(RCT) in-person intervention administered by palliative care clinicians.	Allo and Auto	Caregiver $n = 94$ Patient $n = 160$	Intervention began ~ 72 h of transplant admission and continued 3 months post-transplant.
Fife [24] Objective: Improve cohesion, coping, and communication	(Cohort) Family intervention including two sessions for the dyad, one individual session for the caregiver and 2 DVDs for children.	Allo and Auto	Caregiver $n = 60$ Patient $n = 60$	Intervention began in prior to hospital admission and continued 2–3 weeks following discharge.
Laudenslager et al. [25, 26] and Ouseph et al. [27] Objective: Reduce caregiver distress	(RCT) 8- semi-structured one-on-one sessions with a Master's level social worker (efficacy study of [18•])	Allo	Caregiver $n = 148$	Sessions began on average 2 weeks post-transplant and continued weekly to complete all sessions before the 3-month assessment
Rexilius [28] Objective: Improve depression, anxiety, fatigue, and burden	(Cohort) 30-min massage therapy or healing touch treatments.	Auto	Caregiver $n = 36$	Intervention began during the first week of transplant and continued for 3 weeks.

Auto = Autologous; Allo = Allogenic; RCT = Randomized Control Trial caregiving interventions; some factors that contribute to a risk of bias (e.g., blinding of participants, blinding of outcomes) are unethical and impractical within these interventions. Studies were funded by the National Institutes of Health, the American Cancer Society, and the National Palliative Care Research Foundation.

Are HCT Caregiver Interventions Feasible and Acceptable?

Studies support that HCT caregiver interventions are overall likely to be feasible and acceptable. Studies reported favorable rates of intervention completion (70–100%), indicating that participant retention was feasible. Despite high rates of completion, studies experienced some caregiver attrition due to patient morbidity or mortality [18•, 24]. Authors discussed other barriers to feasibility, including logistical challenges of delivering in-person interventions and planning intervention sessions around caregiver schedules. Several in-person interventions incorporated flexibility into the design. For example, one study allowed for intervention sessions to be attended via teleconference or in-person depending on the caregiver's schedule [22]. A Web-based HCT intervention platform was also deemed acceptable for caregivers in look and feel, content, and feasibility, but posed unique challenges, such as reliance on internet connection, and issues with usability of Web features [17].

Acceptability was demonstrated by objective measures of satisfaction documented by most studies. Among the dyadic (meaning focused on patients and caregivers as a unit) and family-based interventions in this systematic review, there was high satisfaction and acceptability [22, 24]. While, overall, intervention packages were deemed acceptable, some specific components were seen as less so. One study found that while the in-person intervention sessions were acceptable, the use of a biofeedback device for 15 min daily or 4–5 times/week was less acceptable and unreliably used by caregivers [18•].

Are HCT Caregiver Interventions Effective in Optimizing Caregiver Outcomes?

We organized caregiver outcomes into categories: emotional experience, family functioning, coping, well-being/quality of life (QOL), burden, self-reported and objective health, healthcare utilization, and physiological indicators of stress. An evidence map for HCT caregiver interventions is depicted in Table 2.

Emotional Experience

There were mixed effects on outcomes centered on the caregiver's emotional experience including depression, anxiety, and distress. A massage therapy intervention and a multi-session in-person intervention with a social worker both showed positive outcomes for anxiety and depression [25, 28]. Caregivers in a palliative care intervention, compared to controls, reported no significant differences in anxiety or symptoms of major depressive disorder, but had a smaller increase in depression symptoms [23]. A family-based intervention found that the effect size for emotional distress favored the control group, while a problem-solving intervention showed favorable outcomes for distress [22, 24]. Another study found no effect for subjective distress but was effective in reducing a composite score of caregiver distress [25]. A multi-session in-person intervention with a social worker was associated with significantly lower caregiver stress at 3 months post-transplant [22].

Family Functioning

One family-based intervention assessed different domains of family functioning and showed favorable outcomes for cohesion, but no effect for dyadic adjustment. This intervention also showed favorable outcomes for emotional expressiveness within the family environment [24].

Coping

Two interventions assessed coping as an outcome. A palliative care intervention showed improvement in caregiver coping. However, a family-based intervention whose aims were to minimize dysfunctional coping, reduce avoidance, promote communication, and prepare for disruption in family living found no effect on caregiver coping skills [24].

Well-Being and QOL

There were mixed effects on caregiver well-being and QOL. An inpatient palliative care intervention showed favorable outcomes for administrative/financial QOL domains; however, there were no significant effects for overall QOL [23]. Likewise, a multi-session intervention with a social worker found no effect on caregiver well-being [25].

Burden

Two interventions assessed caregiver burden as an outcome, including a massage therapy intervention, and a multi-session intervention with a social worker [25, 28]. Neither intervention found an effect on caregiver burden.

Self-Reported and Objective Health

A multi-session intervention with a social worker found no effect on caregiver sleep quality or well-being [25]. Two

Table 2 Evidence map of intervention effectiveness on caregiver well-being

Intervention Type	Well-being and QOL	Emotional Experience	Family Functioning	Coping	Burden	Physical Health	Healthcare Utilization	Physiological stress
Problem-solving education [22]		↑ (distress) ↑ (self-efficacy)				↑ (fatigue)		
One-on-one sessions with a palliative care clinician [23]	↑ (administrative financial QOL subscore) ↔ (overall QOL)	↔ (anxiety) ↑ (depression) ↔ (symptoms of major depressive disorder)		↑ (coping)				
Family-based intervention [24]		↓ (distress)	↔ (dyadic adjustment) ↑ (cohesion) ↑ (expressiveness within family)	↔ (coping)				
Structured one-on-one sessions with a social worker [25–27]	↔ (composite score of well-being)	↑ (stress) ↑ (depression) ↑ (anxiety) ↑ (mood disturbance) ↑ (composite score of distress) ↔ (distress)			↔ (burden)	↔ (sleep quality)	↑ (mental health use) ↔ (medical service use) ↔ (support group use)	↑ (inflammatory gene expression) ↑ (sympathetic nervous system gene expression) ↑ (oxidative stress gene expression) ↔ (cortisol awakening response)
Massage therapy [28]		↑ (anxiety) ↑ (depression)			↔ (burden)	↑ (fatigue)		

Effect on caregiver outcomes are depicted by arrows: ↑ positive/favorable effect, ↓ negative/unfavorable effect, ↔ no effect studies reported significant reductions in fatigue among caregivers in the intervention compared to those in the control group [22, 28].

Healthcare Utilization

One intervention assessed healthcare utilization as a key outcome [27]. Findings indicate that participation in a psychoeducation, paced respiration, and relaxation intervention, compared to treatment as usual, had favorable effects for decreasing mental health service use, but no significant differences were found between intervention and control groups on medical service utilization or support group utilization.

Physiological Indicators of Stress

One intervention, of moderate quality, consisted of structured one-on-one sessions with a social worker and assessed indicators of objective stress. Compared to caregivers in the control group (voluntary participation in available psychosocial support services at the clinic), caregivers in the intervention group showed significant differences in gene-expression of inflammatory, sympathetic nervous system, and oxidative stress [26]. No significant differences were found between control and intervention conditions for cortisol awakening response as an indicator of stress. (25)

Discussion

This systematic review of HCT caregiver psychosocial interventions suggests that these interventions are generally feasible and acceptable. Most studies reported favorable retention, however, decline in patient health or patient death were common reasons for caregiver attrition. This pattern suggests that when HCT patient health drastically declines or when a patient dies, caregiver participation often wanes and may not be acceptable to caregivers. While transplant-related mortality has decreased, relapse and graft-versus-host disease are the two major causes of mortality [29]. None of the interventions in this review had a unique provision in the protocol for caregivers following changes in patient morbidity (e.g., development of graft-versus-host disease) or mortality. One intervention focused on palliative care, but did not include advance care planning, code status discussions, or end-of-life decision making [23]. Future interventions should incorporate psychoeducation related to patient decline and end of life, and allow for adaptability to the needs of caregivers. Caregivers who drop out of interventions are likely to be the most distressed. Therefore, it is essential to design interventions that retain, not deter, highly distressed caregivers by providing interventions that are adaptable to changes in caregiver distress. It is also important to examine physical and psychosocial outcomes in highly vulnerable bereaved caregivers, given other work in the larger cancer arena showing high prevalence of long-lasting bereavement-related distress among family caregivers [30]. We know little about the experiences of bereaved caregivers of HCT patients, from both scientific and clinical standpoints.

Psychosocial interventions showed favorable yet inconsistent efficacy at addressing caregiver well-being during HCT. Because of the small number of interventions, however, there is insufficient evidence to conclude that one intervention strategy is superior to another or that, compared to a control condition, caregiver interventions are superior at improving any one component of caregiver well-being.

There were inconsistent findings between studies on caregiver emotional experience, with two interventions showing favorable effects on depression and anxiety, and one intervention showing no effect. A similar pattern emerged for caregiver distress, coping, well-being and QOL. No interventions were effective in reducing caregiver burden. One study reported that caregivers reported the most distress but benefitted least from a family-based intervention [24]. This indicates the need to provide unique support to caregivers within the context of family and dyadic interventions.

Based on these findings, we have a number of recommendations. First, the relatively small number of interventions indicates a need for more research with this population in general, with respect to intervention design and development in particular. Second, longer follow-up is needed to ensure the sustainability of intervention outcomes, even if these extend into a bereavement period. HCT challenges extend well beyond the 30–100-day caregiving requirement, and patients may experience transplant-related complications for months or years following HCT. Finally, with only one study in this review using a Web-based platform to deliver an intervention, more research is needed to assess the feasibility and acceptability of health information technology enabled interventions for HCT caregivers. Authors of several studies suggested that feasibility could be improved by alternative intervention delivery, such as smartphones or Web-based platforms [18•, 21]. As tablets and mobile devices become a ubiquitous and preferred mechanism to exchange information, it is essential that research prioritize how the use of technology can support caregivers of cancer patients in the outpatient setting [31]. To ensure such studies reflect the realities of outpatient HCT, it is essential that key stakeholders (patients, caregivers, and providers) be involved in conceptualizing and designing future research [32].

Strengths and Limitations

Strengths of this systematic review include the measures taken to control bias including study screening, quality evaluation, and verification in data extraction. The search strategy was comprehensive using studies from multiple databases. To our knowledge, this is the first systematic review to assess the feasibility, acceptability, and effectiveness of psychosocial interventions on HCT caregiver outcomes. The provided evidence map can facilitate agenda setting for future research in the field.

This review has several limitations. We reviewed a relatively small number of studies. We were not able to conduct meta-analysis and estimate effect size due to substantial heterogeneity in outcome measures across trials. This is largely due to the underdeveloped nature of HCT caregiver interventions. As more interventions are tested, it will be important to review again the HCT intervention research and assess effectiveness. This review did not focus on patient outcomes. As this body of research grows, is imperative that interventions address psychosocial outcomes of both HCT patients and caregivers, and understand the feasibility of intervening with both patients and caregivers [33•].

Conclusion

Psychosocial interventions for HCT caregivers have demonstrated feasibility and acceptability in a small number of available pilot studies. The strength of evidence is insufficient to determine the overall effectiveness of caregiver interventions on improving caregiver outcomes. Psychosocial interventions in this review showed improvements for some caregiver outcomes, but not for others. More research is needed to optimize these interventions. This work can provide insights into intervening with other intensive cancer treatments that require a dedicated caregiver, and therefore has vast implications for understanding how caregivers can provide optimal and sustainable care amidst physically and emotionally challenging cancer treatments.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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