



# Biology of Blood and Marrow Transplantation

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## Reports

### National Institutes of Health Hematopoietic Cell Transplantation Late Effects Initiative: The Patient-Centered Outcomes Working Group Report



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#### A B S T R A C T

In 2015, the National Institutes of Health convened six working groups to address the research needs and best practices for late effects of hematopoietic stem cell transplantation survivors. The Patient-Centered Outcomes Working Group, charged with summarizing the HRQOL evidence base, used a scoping review approach to efficiently survey the large body of literature in adult and pediatric HCT survivors over 1 year after transplantation. The goals of this paper are to (1) summarize the current literature describing patient-centered outcomes in survivors, including the various dimensions of health-related quality of life affected by HCT, and describe interventions tested to improve these outcomes; (2) highlight areas with sufficient evidence allowing for integration into standard practice; (3) address methodological issues that restrict progress in this field; (4) identify major gaps to guide future research; and (5) specify priority research recommendations. Patient-centered outcomes were summarized within physical, psychological, social, and environmental domains, as well as for adherence to treatment, and health behaviors. Interventions to improve outcomes were evaluated for evidence of efficacy, although few interventions have been tested in long-term HCT survivors. Methodologic issues defined included lack of consistency in the selection of patient-centered outcome measures, along with the absence of a standard for timing, frequency, and mode of administration. Recommendations for HCT survivorship care included integration of annual screening of patient-centered outcomes, use of evidence-based practice guidelines, and provision of treatment summaries and survivorship care plans after HCT. Three priority research recommendations included the following: (1) design and test risk-targeted interventions with dose-intensity modulation matching the needs of HCT survivors with priority domains, including sexual dysfunction, fatigue, sleep disruption, nonadherence to medications and recommended health care, health behaviors including physical inactivity and healthy eating, and psychological dysfunction, with particular consideration of novel technologies to reach HCT survivors distant from their transplantation centers; (2) design a consensus-based methodologic framework for outcomes evaluation; and (3) evaluate and compare existing practices for integrating patient-centered outcome screening and interventions across HCT survivorship programs.

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#### INTRODUCTION

Advances in conditioning regimens and supportive care practices and expanded donor sources and cellular therapies have led to expanded access and indications, as well as improved survival rates for hematopoietic stem cell

transplantation recipients [1]. As new populations are exposed to HCT as a potentially curative therapy and survival expectancy lengthens, there is a growing recognition of the adverse impact of treatment on long-term survivorship, including health-related quality of life (HRQOL).

HRQOL is a subjective, multidimensional concept. Although a broad range of life domains can be represented, HRQOL almost universally includes psychological, social, physical (including symptoms), and contextual or environmental aspects of health and illness [2,3]. As a patient-reported outcome (PRO), HRQOL represents an intersection of the individual and his or her culture, values, and preferences relevant to health. As the field has evolved, examining outcomes beyond HRQOL that are patient centered, though not always patient reported, has provided a more comprehensive perspective on the impact of illness on an individual's life [4]. Examples of such outcomes are adherence to medication [5] and health behaviors, such as tobacco use or physical activity [6], which may affect treatment success as well as improve HRQOL.

The impact of HCT on the global HRQOL of survivors has been described in adults [1,7–13] and children [14–19]. Overall, the majority of survivors experience improvement over time, with return to pre-HCT levels of HRQOL by 1 year [10,12,20–22]. Risk factors for poor HRQOL after transplantation include poorer pre-HCT physical health, younger age, depression, female gender, low education level, low social support, physical symptoms, unrelated donor (for childhood HCT), and active chronic graft-versus-host-disease (cGVHD) [22–28]. Despite the overall positive perception of global HRQOL recovery, many survivors report ongoing residual deficits, such as psychological distress, fatigue, sexual dysfunction, cognitive dysfunction, financial toxicity, and cGVHD consequences [22,24,26,29].

Our knowledge regarding the impact of HCT on HRQOL and other patient-centered outcomes is largely derived from studies of the early effects after HCT, rather than long-term or late effects occurring in the years after HCT, and is often limited to those with hematologic malignancies. Since the majority of HCT patients leave the transplantation center and return to their primary providers for long-term care, residual problems can be difficult to follow. This dispersion of survivors also disrupts integrating appropriate services into practice because of challenges in dissemination and implementation of evidence-based care. Moreover, the population of survivors with nonmalignant conditions only recently reached a critical mass, whereby the impact of HCT can be assessed in that set of survivors. The potential chronicity of a nonmalignant condition, the absence of prior cytotoxic therapy, and mild or no graft-versus-host disease may contribute to a different experience compared with those with malignant diseases.

In 2015 the National Cancer Institute and National Heart, Lung, and Blood Institute convened six working groups to address the research needs and best practices for long-term and late effects of hematopoietic stem cell transplantation (HCT) survivors (add [10.1016/j.bbmt.2016.10.020](#)). The Patient-Centered Outcomes Working Group was charged with summarizing the HRQOL evidence base and its integration into practice, as well as identifying key research gaps and opportunities within the HCT survivorship community. The goals of this paper are to (1) summarize the current literature describing patient-centered outcomes in survivors over 1 year after transplantation, including the various dimensions of HRQOL affected by HCT and describe interventions tested to improve these outcomes; (2) highlight areas with sufficient evidence allowing for integration into standard

practice; (3) address methodological issues that restrict progress in this field; (4) identify major gaps to guide future research; and (5) specify priority research recommendations.

## METHODS

A scoping review approach was applied to efficiently survey the large body of literature in adult and pediatric HCT survivors over 1 year after transplantation [30]. Given the breadth of the topic, reviews rather than single studies were preferred. A search of the PubMed database was completed using the following terms: quality of life (HRQOL), psychological (depression, anxiety, distress, uncertainty, worry, post-traumatic stress disorder [PTSD], anger, emotional, mood, and fear of recurrence); social (relationships, isolation, caregiver burden, development, learning, family conflict, dyadic adjustment, support, parents, caregiver, peer); symptoms (pain, neuropathy, fatigue, musculoskeletal, sleep, nausea); function (physical, social, sexual, cognitive, role, work, school); energy (muscle, cardiopulmonary capacity); behaviors (physical activity, adherence, tobacco use, stress management, nutrition); spiritual (existential, purpose, meaning, religion, post-traumatic growth, benefit finding, resilience); financial toxicity; and interventions (pharmacological, nonpharmacological (psycho-educational, cognitive behavioral, stress management, self-management, mindfulness, activity-based, rehabilitation, exercise, yoga, social, web/Internet-based, media, complementary, and alternative). Filters were applied to limit the search to review papers, written in English, and published between January 1, 1990 and November 1, 2015. Quantitative and qualitative studies including adults or pediatric patients undergoing allogeneic or autologous HCT (stem cell transplantation, blood and marrow, BMT, bone marrow) for any indication (malignant or nonmalignant) were included. Secondary search strategies were applied by the working group when review papers were old or not found on a topic. These secondary strategies restricted the literature to survivors 1 or more years after transplantation and expanded the literature to individual studies or studies in other patient populations, eg, general oncology, when necessary.

## FINDINGS

The patient-centered outcomes in this report are presented according to the dimensions of HRQOL (physical, psychological, social, and environmental) and the additional patient-centered outcomes of medical adherence and health behaviors. The estimated prevalence of common outcomes, known risk factors, and comments are summarized in [Table 1](#).

### Physical

Physical symptoms are a major contributor to impairments in HRQOL, including physical and psychological function in HCT survivors [23,31]. Prevalent symptoms reported include pain (particularly musculoskeletal), lack of energy/fatigue, and difficulty with sleep [23]. Although a variety of symptoms have been reported, few have been studied in depth, with little attention to patterns of symptom clusters that are common in cancer patients [32].

### Pain

Pain syndromes have been documented in approximately one-quarter of adult HCT survivors [13,33–36]. Although pain syndromes are not well described, evidence suggests that most pain is correlated with active cGVHD, which is known to be associated with several chronic pain syndromes [24,37–40] as well as avascular necrosis, arthralgias, myalgias, and muscle cramps [13,41]. Adult survivors of childhood HCT report significantly worse bodily pain than healthy matched controls, with 21% reporting persistent pain [38,42].

### Fatigue

Fatigue is among the most common concerns of HCT survivors [7]. Comparisons with age- and gender-matched controls and general population norms have consistently demonstrated greater fatigue in both allogeneic and autologous adult HCT survivors [26,43]. One study found that 35% of allogeneic and autologous transplantation patients were

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