Curr Hematol Malig Rep (2015) 10:213–224
DOI 10.1007/s11899-015-0261-6

HEALTH ECONOMICS (N KHERA, SECTION EDITOR)

The Value of Patient Reported Outcomes and Other Patient-Generated Health Data in Clinical Hematology

Hemant S. Murthy[1] · **William A. Wood**[2]

Published online: 4 June 2015

Abstract With cures and long-term survival rates increasing in hematologic malignancies, increased focus has been placed on gaining a better understanding of the patient experience from disease and treatment effects. This has been the basis for the utilization of patient reported outcomes (PRO) and other patient-generated health data (PGHD) in efforts to improve long-term health-related quality of life (HRQOL). This review will summarize the impact PROs have had on the evolving standard of care for patients with hematologic malignant conditions and will conclude with a template for the integration of PRO and PGHD to enhance the patient experience, using stem cell transplantation as an example.

Keywords Health economics · Hematologic malignancies · Patient reported outcomes · Patient-generated health data · Stem cell transplantation

Introduction

Until relatively recently, many hematologic malignancies were associated with poor prognoses and limited survival. Health-related quality of life (HRQOL), symptoms, and patient functioning during treatment were often secondary concerns. Clinical trials and therapies focused on improving response rates and overall survival, with treatment decisions reliant on laboratory findings, radiographs, and other data obtained during hospitalizations or clinic visits. Life-threatening toxicities were often the primary barriers to therapy. As treatments evolved and survival rates improved, considerations related to the patient experience with cancer and cancer treatment have gained prominence. HRQOL considerations have become especially relevant with regard to optimizing therapies and conducting comparative effectiveness studies of competing therapies. This is particularly important for elderly patients, who must balance risks and benefits of treatments upon different outcomes such as survival, functional independence, and HRQOL [1].

Within hematologic malignancies, there is now an imperative to better understand disease and treatment effects on patients' lives. This has led to increased emphasis on patient reported outcomes (PRO) and other patient-generated health data (PGHD). PRO and other PGHD, whether used independently or in concert with each other, have the potential to generate a picture of a patient's experience outside of a clinical setting from physical, psychological, and social perspectives.

PRO and PGHD in Cancer

Both solid and hematologic malignancies can have adverse effects on patients from both disease effect and therapeutic side effects. These effects can be physical, psychological, and spiritual [2–4]. HRQOL can be compromised at any stage, from diagnosis to long-term cancer survivorship [5].

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

✉ William A. Wood
wawood@med.unc.edu

Hemant S. Murthy
murthyh@ecu.edu

[1] Brody School of Medicine, East Carolina University, 600 Moye Blvd, Greenville, NC 27834, USA

[2] Division of Hematology/Oncology, UNC Lineberger Cancer Center, 101 Manning Drive, Chapel Hill, NC 27514, USA

Defining PRO

PRO, as defined by the United States Food and Drug Administration, is any report of the status of a patient's health condition coming directly from the patient, without interpretation by a clinician or anyone else [6]. PROs measure symptoms, or effects, of a disease or intervention from the patients' perspective alone. The Patient-Reported Outcomes Measurement Information System (PROMIS), a National Institutes of Health funded initiative starting in 2004, is an example of a large effort to systematically standardize and catalogue HRQOL measurements for patients with cancer and other conditions in order to improve clinical care and research for these conditions. A publicly available web-based resource, its creation was meant to create standards for measurements of key health symptoms and HRQOL and to promote and incorporate PROs into research, clinical practice, and policy.

PROs identify disease and therapy effects that are important to patients which may not mirror those perceived to physicians as important or impactful [7, 8]. PROs can evaluate short- and long-term symptom burden and treatment toxicity [9••] and can highlight patient concerns from diagnosis through survivorship, including psychological, emotional, and financial issues. PRO instruments (Tables 1 and 2) may differ by concept measured (e.g., symptoms vs. HRQOL), context (e.g., disease-specific vs. general), construction (e.g., scores, scales, weights), and utility (e.g., mode of data entry, overall ease of use).

Routine PRO collection can improve patient-provider communication, identify and elucidate unrecognized problems, bring positive changes to patient management, and significantly enhance the patient experience [10]. PROs now represent the gold standard method for elicitation of patients' symptoms, HRQOL, and experiences within the oncology context [11•], and prompt intervention from information acquired from PROs in the clinical setting can lead to improved outcomes [12]. Overall improvements in oncologic supportive care and survivorship can be attributed in part to the emphasis placed upon PROs within the field.

Defining PGHD

PGHD is defined as "health-related data—including health history, symptoms, biometric data, treatment history, lifestyle choices, and other information—created, recorded, gathered, or inferred by or from patients or their designees (i.e., care partners or those who assist them) to help address a health concern [13]. PGHD includes PROs, but also other data streams generated by patients and often captured by sensors and wearable devices. Examples of PGHD streams include steps, heart rate, caloric expenditure, sleep, and temperature. Commercial wearables that capture PGHD include devices manufactured by Fitbit, Jawbone, Apple, and others.

PGHD can be collected frequently, over long periods of time and outside of clinical encounters [14•]. In addition to data captured by sensors, PGHD can also be obtained through patient data entry, such as information related to mood, social history, or medication adherence.

Though the ultimate impact of this data is unknown, PGHD integration with the electronic medical record is likely. The NIH, through the Big Data to Knowledge Initiative, as well as other large collaborations such as the National Patient-Centered Research Network (PCORnet) is working towards the application of these data for the enhancement of health care. PGHD might help to inform disease or treatment prognostic models, identification of risk of adverse outcomes, and perhaps matching patients with appropriate clinical trials based on eligibility criteria [15].

Impact of PRO Within Hematologic Malignancies

As survival rates improve in hematologic malignancies and patients encounter an increasing array of treatment options, new questions emerge. Which therapies optimize long-term quality of life? Are new therapies superior to best supportive care from a patient perspective, when survival differences between approaches are modest? What unforeseen problems are long-term survivors experiencing? For these questions, patient-reported outcomes have helped provide some guidance, which in some circumstances have been practice changing.

Symptom Burden and Interventions

To understand the full impact of a disease, the patient's perspective is crucial. Patient and clinician perspectives do not always align [8, 16, 17]. Elicitation of symptom burden depends partly on the PRO instrument used. The information gained from PROs can be used clinically to direct interventions designed to improve symptoms and ultimately HRQOL.

In multiple myeloma, validated cancer-specific (EORTC QLQ-30) and disease-specific (EORTC QLQ-MY20) PROs have helped identify deleterious effects of myeloma with regard to symptoms as well as disease-specific emotional effects [18]. PROs can also facilitate the evaluation of supportive measures such as erythropoietin-stimulating agents (ESA). ESAs were shown to significantly improve emotional, physical, social, and sleep quality of life as measured by a general health PRO, the Nottingham Health Profile, and reduce fatigue as measured by a symptom-specific PRO, the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) [19–21].

Table 1 General and cancer-specific PRO tools used in hematology [9••, 11•]

PRO instrument	Item measured	Description
SF 36	General quality of life	8 scaled scores that measure fatigue, physical functioning, and limitations on physical, emotional and social functioning, pain, general health and mental health. One of the most frequently used Quality of Life questionnaire in hematology
WHO-QOL 100	General quality of life	Overall quality of health, physical health, psychological health, functional independence, interpersonal relationships, financial impact of disease, and spiritual health
Nottingham Health Profile	General quality of life	Centered on health including pain, energy, sleep, mobility, emotional reaction, and social isolation as well as life areas affected such as occupation, housework, social life, family life, sexual function, hobbies, and holidays.
MDASI	General symptom assessment	13 core symptoms (pain, fatigue, nausea, sleep, emotional distress, dyspnea, appetite, drowsiness, dry mouth, sadness, vomiting, neuropathy, cognitive impairment) and 6 interference items (activity, mood, walking, work, life enjoyment, personal relations) Disease-specific versions available include CML, myeloma, cGVHD
Edmonton Symptom Assessment System (ESAS)	General symptom assessment	Symptoms assessment (tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath) primarily utilized in palliative care setting
Memorial Symptom Assessment Scale (MSAS)	General symptom assessment	Measurement of 32 different symptoms over 3 major groups (psychological, high-prevalence physical and low-prevalence physical symptoms) based on its severity, frequency, and the distress caused.
PRO-CTCAE	Cancer specific	Patient-related outcome version of the NCI Common Terminology Criteria for Adverse Events (CTCAE). Up to 78 adverse events measured, each event then quantifying frequency, severity, and/or activity interference. Can be administered via the internet or telephone
EORTC QLQ-30	Cancer specific	General cancer quality of life, divided into categories (physical, role, emotional, social, cognitive, and financial impact. Disease-specific versions including leukemia (QLQ-Leu), multiple myeloma (QLQ-MY20) and Hodgkin lymphoma (H8 LQ)
FACT-G	Cancer specific	General quality of life specific to cancer patients, 4 well-being categories including physical, social/family, emotional, and functional. Disease-specific versions used in conjunction with FACT-G include FACT-MM (myeloma), FACT-BMT (bone marrow transplant), FACT-Leu (leukemia), NCCN-FACT FLymSI-18 (lymphoma)

Table 2 Disease- and symptom-specific PRO tools used in hematology [9••, 11•]

PRO instrument	Item measured	Description
EORTC-MY20	Disease-specific multiple myeloma	20-Item QOL assessment tool, addressing location and severity of pain, neuropathy, fatigue, thirst, alopecia, and questions relating to fears about illness and mortality
Quality of life in myelodysplasia scale (QUALMS-1)	Disease-specific myelodysplastic syndrome	33-Item QOL assessment tool. 12 domains including fatigue, emotional health, uncertainty, disease information, family relationships, non-fatigue symptoms, financial, hope, social functioning, sexual health and self-image
QOL-E v.2	Disease-specific myelodysplastic yndrome	MDS specific measuring physical, functional, social, sexual domains, fatigue, and MDS-specific domains (dyspnea, transfusion dependence, ADLs, concern about disease, treatment side effects, and dependence on medical staff)
MF-SAF	Disease-specific myelofibrosis	Initially a 20-item instrument, v2.0 streamlined electronic PRO developed for COMFORT-1 trial, comprised of 7 questions assessing night sweats, pruritus, abdominal discomfort, splenic pain, early satiety, myalgias, and inactivity
MPN-SAF	Disease-specific myeloproliferative neoplasm	Adapted from MF-SAF with additional questions added, including concentration, headaches, dizziness, numbness/tingling, insomnia, depression, and sexual dysfunction. Co-administered with BFI for assessment of fatigue
FACT-An	Symptom-specific anemia	Consists of FACT-G and 16 specific anemia questions relating to symptoms, effect on activities, frustrations, and impact on social activities. Utilized in cancer-related anemia as well as MDS
Functional Assessment of Cancer Therapy-Fatigue (FACT-F)	Symptom-specific fatigue	Consists of 13 items dealing with fatigue (fatigue, weakness, listlessness, tiredness, energy, and ability to perform daily activities, limitation of social activities, and need of sleep during the day).
Brief fatigue inventory (BFI)	Symptom-specific fatigue	Assesses impact and severity of cancer-related fatigue and impact on activity, mood, ambulation, work, relations, and life enjoyment
FACT-GOG/neurotoxicity (NTX)	Symptom-specific neuropathy	Consists of FACT-G and 10 neuropathy-specific questions. Used in patients specifically with bortezomib neurotoxicity
FACT-BMT	Treatment-specific bone marrow transplant	Comprised of FACT-G and 23 specific BMT questions regarding physical symptoms, BMT-related concerns and social and family effect (including employment, financial, sexuality, family burden, fertility)
FACT-biologic response modifiers	Treatment-specific biologic modifiers	Specific for patients on biologic response modifiers. Initially used for patients on interferon therapy and now has been used for tyrosine kinase inhibitors for CML.
Comprehensive score for financial toxicity (COST-FACIT)	Treatment-specific financial toxicity	Specific for financial concerns and impact of cost of oncology care on patients. 11 questions total measuring cost of treatment, out-of-pocket expenses, future financial worries, lack of fiscal control, able to meet monthly expenses, financial stress, financial satisfaction, employment frustration

Ideally, the same PRO can identify significant impairment in HRQOL and can monitor the change attributed to a particular intervention. For example, the symptom-specific Functional Assessment of Cancer Therapy-Anemia (FACT-An) has been utilized in myelodysplastic syndrome to quantitate symptom burden and HRQOL [22]. The FACT-An has also been used to show the ability of ESAs to ameliorate symptoms, reduce transfusion requirements, and improve HRQOL [23, 24].

Using PROs to Compare Treatment Alternatives in Hematologic Malignancies

PROs have been used to compare management strategies for patients with hematologic malignancies. One prominent example of this was imatinib for chronic myeloid leukemia (CML). Prior to 2003, treatment options for CML were limited to interferon-based chemotherapy, hydroxyurea, and stem cell transplantation. The IRIS trial in 2003 ushered in tyrosine kinase inhibitor (TKI)-based therapy for CML and transformed CML into a chronic condition associated with long-term survival. Imatinib demonstrated superior response rates and lower rates of progression to accelerated and blast phases in comparison with treatment alternatives [25]. PROs collected in the UK MRC CML 3 trial and the IRIS trial were able to highlight the difference in HRQOL between interferon-based therapy and imatinib. The UK MRC CML 3 trial used the EORTC QLQ 30 to demonstrate significantly worse pain and dyspnea, as well as worse social, emotional, and cognitive functioning with interferon therapy compared to non-IFN therapy [26]. Meanwhile, using Euro QoL-5D and therapy-specific PRO, the FACT-Biologic Response Measure (FACT-BRM), patients enrolled on the IRIS trial receiving imatinib reported better daily functioning, less fatigue, and fewer side effects compared to interferon therapy, as well as significant improvement in HRQOL for patients who crossed over from interferon to imatinib [27].

Subsequent to imatinib's approval, newer TKIs have been developed for first-line CML treatment, including dasatinib and nilotinib. While these have produced improved cytogenetic and molecular response rates [28, 29], overall survival estimates among the agents have been similar [30]. In this setting, PROs have provided complementary information from the patient perspective. Thus far, PRO studies have demonstrated similar outcomes among TKIs with respect to depression, symptom burden, and decline in HRQOL [31, 32], though nilotinib has been found in at least one study to be reported as more difficult to take, leading to worse treatment adherence in comparison with other agents [33].

PROs have helped compare treatment approaches in multiple myeloma, a disease of plasma cells characterized by skeletal destruction and other events with significant impact upon the patient experience. Within myeloma, patient-reported fatigue, pain, and overall HRQOL using instruments such as the EORTC-QLQC30, EORTC QLQ-MY24, and FACT-GOG-Ntx (among others) have been found to be prognostic for survival, whether these data were obtained before or after treatment [34]. With competing treatment strategies available for multiple myeloma that include proteasome inhibitors, immunomodulatory agents, and high-dose chemotherapy (in the context of autologous stem cell transplantation), PROs provide information that assists in risk/benefit calculations for each agent from the patient perspective [9••]. One example is bortezomib, which was compared to dexamethasone in the phase 3 APEX trial for relapsed/refractory multiple myeloma. Prospectively collected PROs (EORTC QLQ 30, FACT-GOG-Ntx) showed that physical, emotional, role functioning, and cognitive health as well as symptoms such as fatigue, sleep, and diarrhea improved with bortezomib, although neurotoxicity was increased [35]. The addition of bortezomib to melphalan-prednisone (VMP) for elderly transplant ineligible patients in the phase 3 VISTA trial was associated with an improvement in HRQOL compared to melphalan and prednisone (MP), measured by the EORTC QLQ C30. However, this analysis also showed initially decline in HRQOL with the first four cycles of VMP, leading to subsequent strategies in dose adjustment and scheduling of bortezomib and finding that lower doses resulted in improved HRQOL [36, 37]. Comparing intravenous and subcutaneous routes of bortezomib administration, clinical outcomes including overall survival were similar, but PROs demonstrated improved in peripheral neuropathy and increased overall satisfaction when subcutaneous administration [38, 39]. Another example is immunomodulatory agents in myeloma. PROs showed thalidomide's lack of improvement in HRQOL when added to MP for elderly patients compared to MP alone [37, 38, 40] and an NCIC-CTG trial of maintenance thalidomide and prednisone versus placebo following stem cell transplantation was associated with worse HRQOL [41]. Lenalidomide, on the other hand, showed improved HRQOL when used in combination with MP compared to MP alone in the MM-015 trial and also improved HRQOL in comparison with placebo maintenance [42, 43]. The FIRST trial, comparing thalidomide and MP with lenalidomide and dexamethasone showed overall HRQOL improved in both groups, though specific patient-reported adverse treatment effects differed [44].

Acute promyelocytic leukemia (APL) represents another disease in which two strategies with similar clinical outcomes differed in HRQOL, highlighted using PROs. All trans retinoic acid (ATRA) and anthracycline chemotherapy, a standard treatment approach, was recently compared in a phase 3 study to ATRA and arsenic for the management of low- and intermediate-risk APL [45]. Though ATRA and arsenic strategy was non-inferior with respect to survival, PRO data using the EORTC QLQ-C30 demonstrated superior HRQOL in the arsenic group, with fatigue showing the largest between-group

difference [46]. This PRO difference has been used to support arsenic-based therapy as first-line treatment for low- to intermediate-risk APL.

Using PROs to Compare New Therapies with Best Supportive Care

Among older patients or those with poor performance status, new therapies may be associated with adverse effects that are intolerable; however, new treatment approaches with less toxicity may offer better HRQOL even in the absence of significant survival prolongation in comparison with best supportive care. Integrating general or disease-specific PROs into the regulatory approval process may help develop therapies with beneficial effects upon the patient experience. Two examples of this approach include myelofibrosis (MF) with the Jak2 inhibitor, ruxolitinib, and myelodysplastic syndrome (MDS) with hypomethylating agents such as azacitadine and decitabine.

The development of ruxolitinib in myelofibrosis illustrates PRO's impact in drug approval for a condition which best supportive care was the previously accepted standard. Because no myelofibrosis-specific PRO existed, the 20-item Myelofibrosis Symptom Assessment Form (MF-SAF) was developed for use in therapeutic clinical trials based on surveys of patients with myelofibrosis [47]. The MFSAF, EORTC QLQ-30, and PROMIS-fatigue was used in the COMFORT-1 trial to demonstrate an HRQOL benefit for ruxolitinib in comparison with placebo [48, 49] and in COMFORT-2 trial a HRQOL benefit in comparison with best available therapy, including hydroxyurea, steroids, ESA, and immunomodulatory drugs such as thalidomide and lenalidomide [50, 51]. Largely due to improvement measured by PRO, including the myelofibrosis total symptom score, ruxolitinib was approved by the FDA in 2011 for symptomatic myelofibrosis [52] and remains one of the only cancer therapeutics in which the beneficial effects of a drug on patient symptoms are included in the US drug label [53•].

Myelodysplastic syndrome (MDS) is a disease characterized by impaired bone marrow function and transformation to acute leukemia [54]. Most patients with MDS have impaired HRQOL due symptomatic anemia and transfusion requirements, mental and physical fatigue, and emotional distress [55]. Previously, standard of care for MDS was supportive treatment only, with few studies showing HRQOL improvements with patients treated erythropoietin-stimulating agents (ESAs) so long as response was demonstrated to these agents [24, 56]. Azacitadine, a hypomethylating agent with activity in myelodysplastic syndrome, was shown in a CALGB phase 3 study to improve response rate and overall survival in comparison with supportive care for high-risk MDS [57]. Using PROs such as EORTC QLQ-C30 and the mental health inventory (MHI), azacitadine demonstrated significant improvement in fatigue, physical functioning, dyspnea, positive affect, and psychological distress in comparison with supportive care [57, 58]. Similar HRQOL benefits were demonstrated in phase 3 studies involving decitabine, resulting in increased utilization of hypomethylating agents in patients with high-risk MDS [59, 60].

A recently developed MDS-specific PRO, the QUALMS-1 was validated as a measure of disease-specific quality of life in MDS [61] with an expressed hope for use in facilitating approval of new disease-modifying therapies, allowing physicians to advise patients about risks and benefits of MDS therapies in the context of their quality of life [62]. The MFSAF for MF and the QUALMS-1 for MDS represent recent examples within hematologic malignancies of how disease-specific PROs may be developed to assist drug development and research design in studies of different conditions [53•].

PROs as Prognostic Markers

Multiple studies in oncology have demonstrated that PROs provide useful prognostic information. A retrospective study of nearly 40 solid tumor clinical trials showed that PROs were prognostic for survival, at times more predictive of overall survival than traditionally measured performance status [63]. In a recent secondary analysis of BMT CTN 0902, a randomized study of exercise and stress management training prior to HSCT, investigators found that patients with lower pre-HSCT physical HRQOL and early declines in HRQOL experienced worse overall survival and increased transplant-related mortality [64]. In another study, Thompson and colleagues used the FACT-G in patients with newly diagnosed aggressive lymphomas to show an association of low-baseline HRQOL scores with inferior overall survival, even after adjusting for other factors such as age and IPI [65]. An ongoing study, the PROMYS study (CinicalTrials.gov identifier NCT00809575), an international multi-center trial, is studying the impact of changes detected via PRO on overall survival in patients with newly diagnosed MDS and is scheduled to complete in 2018.

The Use of PROs When Treatment Is Completed

As cures and long-term remissions in hematologic malignancies become more commonplace, new and often-unforeseen symptoms and QOL issues have been identified. Many long-term effects and survivorship issues have been identified in recent years from information gathered using PROs from survivors.

Hodgkin lymphoma represents one hematologic malignancy with relatively high rates of long-term remission and survival [66, 67]. Prospectively collected PROs for early-stage Hodgkin lymphoma patients enrolled on the SWOG 9208 helped highlight short- and long-term impairments in HRQOL, including fatigue, which persist several years following treatment [68]. Another study showed survivors of

Hodgkin lymphoma reporting impairments in physical functioning, performing work and daily activities, sexual function, and increased financial and employment burdens 10–18 years following initial therapy [69].

These effects are not limited to Hodgkin survivors. Fatigue, pain, sexual dysfunction, decline in emotional and role functioning, financial impairment, and difficulty gaining employment were seen across survivors of lymphomas, acute myeloid leukemia, and acute lymphoblastic leukemia, including childhood cancer survivors [70–72]. With treatments for hematologic malignancies becoming more expensive, PROs have highlighted the financial consequences of cancer and cancer treatment on patients. Though studies have shown therapies such as imatinib and bortezomib may be cost-effective from the perspective of quality-adjusted life years [73, 74], these analyses may not fully account for patient concerns related to finances and employment [68, 71]. A new term, "financial toxicity," has recently been developed to account for issues like these [75]. Some PROs have included financial and employment domains, such as the WHO-QOL and FACT-BMT, and more recently a PRO specific for financial concerns, comprehensive score for financial toxicity (COST), was developed and validated for these specific concerns [76].

Integrating Other PGHD with PROs: the Example of Hematopoietic Cell Transplantation

Increasingly, other types of PGHD have become available to complement PROs in providing a more complete patient-centered assessment that includes objective data related to patient functioning. Hematopoietic cell transplantation (HSCT) may provide a template for how PROs and other types of PGHD might become integrated within the hematologic malignancies.

Pre-transplantation Assessments

Currently, pre-transplant assessments are used to risk stratify patients prior to undergoing HSCT to predict those at higher risk of treatment-related toxicity, to inform risk/benefit assessments and to aid clinical decision making. These assessments are particularly important as more transplants are being performed in patients over the age of 60. Commonly measured by the clinician-assessed ECOG or Karnofsky Performance Status (KPS), functional status has consistently predicted non-relapse mortality and overall survival among transplant patients [77]. However, functional status has traditionally been clinician assessed and not patient reported or patient generated, thus lacking sufficient sensitivity to fully reflect patient functioning and to discriminate among those with marginal reserve. Most standard pre-transplant assessment measures, such as the HCT-CI [78] and the EBMT risk score [79], do not include patient-reported or patient-generated information [80]. Recent studies have shown that information derived from 6-min walk tests (6MWT) [81] or cardiopulmonary exercise tests (CPET) [82] can measure pre-transplant fitness with increased precision, potentially adding to pre-transplant assessments. Wearable devices with integrated accelerometers may further complement patient-generated data derived from exercise tests to provide a more complete picture of functional status [83]. Several of these devices now have published data validating core functions such as step count and energy expenditure [84, 85], which in turn have been correlated with HRQOL and comorbidities [86]. Further work is needed to validate these devices in cancer patients and to ensure acceptable usability in this population [83]. However, once validated and acceptable, wearable devices that measure physical activity have the promise to aid pre-transplant functional assessments and potentially to inform pre-, peri-, or post-transplant exercise prescriptions [94–96].

Peri- and Post-Transplant Complications

Many long-term effects on HRQOL from transplant arise during the peri-transplant or early post-transplant period. Some complications may benefit from early recognition to limit long-term chronic impairment. For this and because some transplants are now performed on an outpatient basis, PRO and PGHD can play a role in improving outcomes when used in these periods.

Insomnia is a frequent complication of HSCT, mostly occuring during the peri-transplant period [87, 88], and associated with decreased physical functioning, increased fatigue, poor psychological well-being, and increased inflammation [88, 89]. Actigraphy has been utilized as a reliable and valid instrument for sleep assessment. Newer wearable devices with actigraph function have demonstrated correlations with polysomnography in measuring total sleep time and sleep efficiency [90]. Monitoring of sleep wake cycles using actigraphs as well as PROs may help in detecting early complications of HSCT and in managing sleep disturbances during transplant [89, 91].

Other complications of HSCT which can impair HRQOL include acute or chronic graft versus host disease, pulmonary toxicities, fatigue, anxiety, depression, cognitive impairment, and reduced physical function [92–98]. Electronic patient reported outcomes (ePRO) can help recognize and address these concerns. Frequent ePRO collection during HSCT has shown to be feasible and acceptable with patients of different ages, levels of education, and types of transplant [99]. ePRO can be conducted from clinic or home, via telephone or the web, using computers, tablets, and smart phones, allowing for frequent assessments and monitoring of expected and unexpected toxicities [100, 101] with high rates of compliance [48]. Cost benefit of ePRO collection in transplant and ePRO ability to potentially improve outcomes in patients living long distances from their transplant centers remain to be studied and addressed [102].

Patient-Reported Experience Measures (PREM)

We anticipate that PROs and PGHD will continue to become more integral components of research and clinical practice in hematologic malignancies and HSCT. To these categories of patient-reported data, we also anticipate that a third important category, Patient Reported Experience Measures (PREMs), will also assume importance. Similar to PROs, PREMs are reports directly from the patient, in this case measuring a patient's experience with care delivery. Examples of care delivery metrics include trust in physicians, adequacy of pain control, experience with hospitalization, and adequacy of facilities and supportive care measures. We anticipate that PREMs are highly likely to impact PROs, with subsequent attendant affects upon HRQOL and overall survival. In the context of hematologic malignancies and transplantation, which are longitudinal inpatient and outpatient experiences with the health care system that span many months to years, we expect that PREMs will be particularly important. Further research into measurement methodology, predictive modeling, and intervention planning utilizing PREMs is needed.

Incorporating Into Clinical Practice—an Evolving Paradigm

Integrating and incorporating PROs, PREMs, and PGHD into everyday clinical practice remains a concern. PROs can provide meaningful information along the cancer continuum, from diagnosis through survival (Fig. 1). Less studied however is how to integrate PRO efficiently into care delivery. Frequent collection of PRO is feasible [99], and with new technologies such as wearable-derived PGHD, information available to clinicians will increase exponentially. Research moving forward should develop and compare alternative approaches to bringing PROs into practice. Should PROs be delivered to clinicians at the time of clinic visits, from the waiting room, or between visits, with electronic home-based collection or PGHD transmission? Should this information go directly to primary clinicians, or to an intermediary? Can we envision a new class of consultants who monitor patient-reported data, coach and advise patients in order to positively impact functional status between visits, and summarize this information in reports for clinicians? Innovative models like this may be needed to optimize use of patient-reported data in clinical practice.

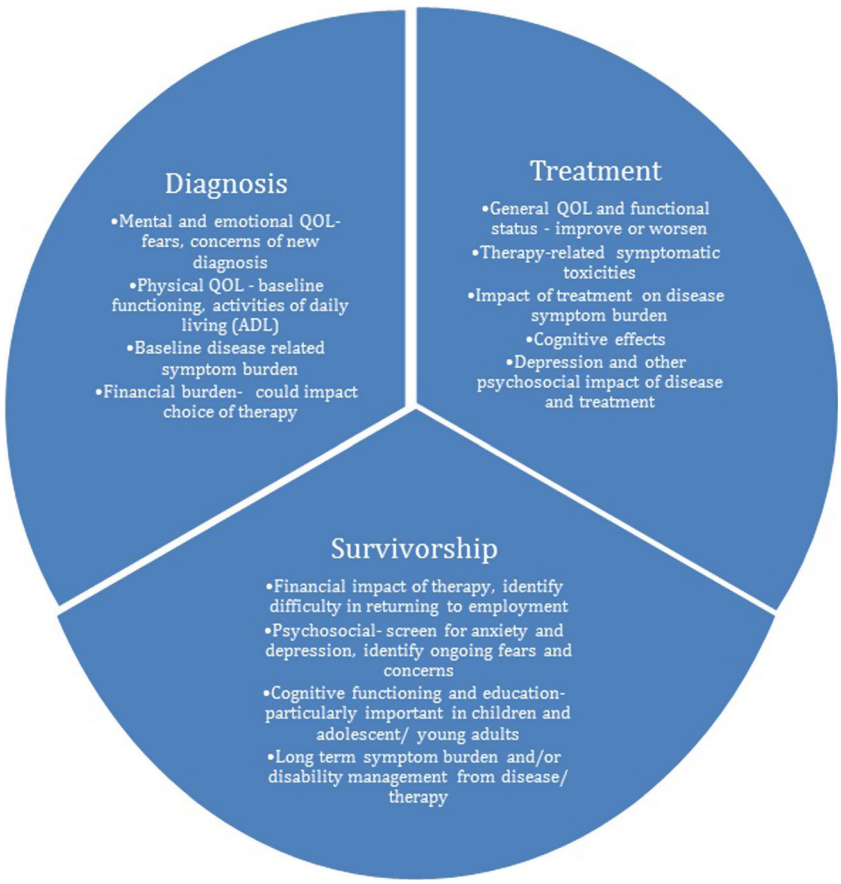

Fig. 1 Integration of PRO in cancer continuum

Conclusions

PROs have helped improve the care of patients with hematologic malignancies, gaining importance as long-term survival rates continue to improve. Our treatment approaches for many conditions have been impacted by information provided directly by patients themselves. New data acquisition methods of PGHD provides new opportunities, in conjunction with PRO, for improving assessments of patient functioning and increasing awareness of the disease and treatment burden experienced by patients. With this information in hand, we will be able to further improve outcomes for patients with these diseases, from diagnosis through survivorship.

Compliance with Ethics Guidelines

Conflict of Interest Hemant S. Murthy and William A. Wood each declare no potential 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.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance
- ?

1. Efficace F, Novik A, Vignetti M, Mandelli F, Cleeland CS. Health-related quality of life and symptom assessment in clinical research of patients with hematologic malignancies: where are we now and where do we go from here? Haematologica. 2007;92(12):1596–8.
2. Cheng KK, Yeung RM. Impact of mood disturbance, sleep disturbance, fatigue and pain among patients receiving cancer therapy. Eur J Cancer Care (Engl). 2013;22(1):70–8.
3. Peteet JR, Balboni MJ. Spirituality and religion in oncology. CA Cancer J Clin. 2013;63(4):280–9.
4. Spiegel D, Riba MB, DeVita VT, Lawrence TS, Rosenberg SA. In: DeVita H, editor. Rosenberg's cancer: principles & practice of oncology. 9th ed. Philadelphia: LIPPINCOTT WILLIAMS & WILKINS; 2011. p. 2467–76.
5. Badr H, Chandra J, Paxton RJ, Ater JL, Urbauer D, Cruz CS, et al. Health-related quality of life, lifestyle behaviors, and intervention preferences of survivors of childhood cancer. J Cancer Surviv. 2013;7(4):523–34.
6. United States Department of Health and Human Services Food and Drug Administration. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf. Accessed Feb 1 2015: United States Department of Health and Human Services Food and Drug Administration; 2009 December 2009.
7. Oliva EN, Finelli C, Santini V, Poloni A, Liso V, Cilloni D, et al. Quality of life and physicians' perception in myelodysplastic syndromes. Am J Blood Res. 2012;2(2):136–47.
8. Efficace F, Rosti G, Aaronson N, Cottone F, Angelucci E, Molica S, et al. Patient- versus physician-reporting of symptoms and health status in chronic myeloid leukemia. Haematologica. 2014;99(4):788–93.
9. •• Guidelines Patient-Reported Outcomes in Hematology. 1st ed. Novik A, Salek S, Ionova T, editors. The Hague, The Netherlands: European Hematology Association Scientific Working Group "Quality of Life and Symptoms"; 2012. **Guidelines published by the EHA, details the standards for acceptance and validation of PRO, and reviews and summarizes PROs by hematologic condition both benign and malignant, along with brief description of each PRO**.
10. Chen J, Ou L, Hollis SJ. A systematic review of the impact of routine collection of patient reported outcome measures on patients, providers and health organisations in an oncologic setting. BMC Health Serv Res. 2013 Jun 11;13:211,6963-13-211.
11. • Basch E, Abernethy AP, Mullins CD, Reeve BB, Smith ML, Coons SJ, et al. Recommendations for incorporating patient-reported outcomes into clinical comparative effectiveness research in adult oncology. J Clin Oncol. 2012;30(34):4249–55. **Describes general recommendations for use of PRO in clinical oncology research when comparing effectiveness of therapeutics. Table 2 shows PROs specifically recommended based on prior use in oncology trials and compares based on symptoms assessed**.
12. Ediebah DE, Coens C, Zikos E, Quinten C, Ringash J, King MT, et al. Does change in health-related quality of life score predict survival? Analysis of EORTC 08975 lung cancer trial. Br J Cancer. 2014;110(10):2427–33.
13. Shapiro M, Johnston D, Wald J, Mon D. Patient-generated Health Data: White Paper Prepared for the Office of the National Coordinator for Health it by RTI International. Available at http://www.rti.org/pubs/patientgeneratedhealthdata.pdf. RTI International 3040 Cornwallis Road Research Triangle Park, NC 27709: RTI international; 2012 April 2012.
14. • Wood WA, Bennett AV, Basch E. Emerging uses of patient generated health data in clinical research. Mol Oncol. 2014 Aug 27. **Summarizes patient generated health data, identifies new datastream sources and quantifiable measures, and describes its potential applications in clinical trials and oncology**.
15. Shah ND, Pathak J. Why Health Care May Finally be Ready for Big Data. Harvard Business Review. 2014 December 3, 2014;https://hbr.org/2014/12/why-health-care-may-finally-be-ready-for-big-data.
16. Efficace F, Breccia M, Saussele S, Kossak-Roth U, Cardoni A, Caocci G, et al. Which health-related quality of life aspects are important to patients with chronic myeloid leukemia receiving targeted therapies and to health care professionals? GIMEMA and EORTC Quality of Life Group. Ann Hematol. 2012;91(9):1371–81.
17. Di Maio M, Gallo C, Leighl NB, Piccirillo MC, Daniele G, Nuzzo F, et al. Symptomatic Toxicities Experienced During Anticancer Treatment: Agreement Between Patient and Physician Reporting in Three Randomized Trials. J Clin Oncol. 2015 Jan 26.
18. Cocks K, Cohen D, Wisloff F, Sezer O, Lee S, Hippe E, et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-MY20) in assessing the quality of life of patients with multiple myeloma. Eur J Cancer. 2007;43(11):1670–8.
19. Dammacco F, Castoldi G, Rodjer S. Efficacy of epoetin alfa in the treatment of anaemia of multiple myeloma. Br J Haematol. 2001;113(1):172–9.
20. Kvam AK, Fayers P, Hjermstad M, Gulbrandsen N, Wisloff F. Health-related quality of life assessment in randomised controlled trials in multiple myeloma: a critical review of methodology and

impact on treatment recommendations. Eur J Haematol. 2009;83(4):279–89.
21. Hedenus M, Adriansson M, San Miguel J, Kramer MH, Schipperus MR, Juvonen E, et al. Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: a randomized, double-blind, placebo-controlled study. Br J Haematol. 2003;122(3):394–403.
22. Jansen AJ, Essink-Bot ML, Beckers EA, Hop WC, Schipperus MR, Van Rhenen DJ. Quality of life measurement in patients with transfusion-dependent myelodysplastic syndromes. Br J Haematol. 2003;121(2):270–4.
23. Clavio M, Nobili F, Balleari E, Girtler N, Ballerini F, Vitali P, et al. Quality of life and brain function following high-dose recombinant human erythropoietin in low-risk myelodysplastic syndromes: a preliminary report. Eur J Haematol. 2004;72(2):113–20.
24. Spiriti MA, Latagliata R, Niscola P, Cortelezzi A, Francesconi M, Ferrari D, et al. Impact of a new dosing regimen of epoetin alfa on quality of life and anemia in patients with low-risk myelodysplastic syndrome. Ann Hematol. 2005;84(3):167–76.
25. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2003;348(11):994–1004.
26. Homewood J, Watson M, Richards SM, Halsey J, Shepherd PC. Adult Leukaemia Working Party. Treatment of CML using IFN-alpha: impact on quality of life. Hematol J. 2003;4(4):253–62.
27. Hahn EA, Glendenning GA, Sorensen MV, Hudgens SA, Druker BJ, Guilhot F, et al. Quality of life in patients with newly diagnosed chronic phase chronic myeloid leukemia on imatinib versus interferon alfa plus low-dose cytarabine: results from the IRIS Study. J Clin Oncol. 2003;21(11):2138–46.
28. Kantarjian HM, Hochhaus A, Saglio G, De Souza C, Flinn IW, Stenke L, et al. Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. Lancet Oncol. 2011;12(9):841–51.
29. Jabbour E, Kantarjian HM, Saglio G, Steegmann JL, Shah NP, Boque C, et al. Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION). Blood. 2014;123(4):494–500.
30. Heaney ML. Sequencing treatment in chronic myeloid leukemia: the first choice may be the hardest. Clin Adv Hematol Oncol. 2014;12(8):502–8.
31. Phillips KM, Pinilla-Ibarz J, Sotomayor E, Lee MR, Jim HS, Small BJ, et al. Quality of life outcomes in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors: a controlled comparison. Support Care Cancer. 2013;21(4):1097–103.
32. Efficace F, Cardoni A, Cottone F, Vignetti M, Mandelli F. Tyrosine-kinase inhibitors and patient-reported outcomes in chronic myeloid leukemia: a systematic review. Leuk Res. 2013;37(2):206–13.
33. Hirji I, Gupta S, Goren A, Chirovsky DR, Moadel AB, Olavarria E, et al. Chronic myeloid leukemia (CML): association of treatment satisfaction, negative medication experience and treatment restrictions with health outcomes, from the patient's perspective. Health Qual Life Outcomes. 2013 Oct 8;11:167,7525-11-167.
34. Wisloff F, Hjorth M. Health-related quality of life assessed before and during chemotherapy predicts for survival in multiple myeloma. Nordic Myeloma Study Group. Br J Haematol. 1997;97(1):29–37.
35. Lee SJ, Richardson PG, Sonneveld P, Schuster MW, Irwin D, San Miguel JF, et al. Bortezomib is associated with better health-related quality of life than high-dose dexamethasone in patients with relapsed multiple myeloma: results from the APEX study. Br J Haematol. 2008;143(4):511–9.
36. Delforge M, Dhawan R, Robinson Jr D, Meunier J, Regnault A, Esseltine DL, et al. Health-related quality of life in elderly, newly diagnosed multiple myeloma patients treated with VMP vs. MP: results from the VISTA trial. Eur J Haematol. 2012;89(1):16–27.
37. Sonneveld P, Verelst SG, Lewis P, Gray-Schopfer V, Hutchings A, Nixon A, et al. Review of health-related quality of life data in multiple myeloma patients treated with novel agents. Leukemia. 2013;27(10):1959–69.
38. Barbee MS, Harvey RD, Lonial S, Kaufman JL, Wilson NM, McKibbin T, et al. Subcutaneous versus intravenous bortezomib: efficiency practice variables and patient preferences. Ann Pharmacother. 2013;47(9):1136–42.
39. Moreau P, Pylypenko H, Grosicki S, Karamanesht I, Leleu X, Grishunina M, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. Lancet Oncol. 2011;12(5):431–40.
40. Waage A, Gimsing P, Fayers P, Abildgaard N, Ahlberg L, Bjorkstrand B, et al. Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma. Blood. 2010;116(9):1405–12.
41. Stewart AK, Trudel S, Bahlis NJ, White D, Sabry W, Belch A, et al. A randomized phase 3 trial of thalidomide and prednisone as maintenance therapy after ASCT in patients with MM with a quality-of-life assessment: the National Cancer Institute of Canada Clinicals Trials Group Myeloma 10 Trial. Blood. 2013;121(9):1517–23.
42. Dimopoulos MA, Delforge M, Hajek R, Kropff M, Petrucci MT, Lewis P, et al. Lenalidomide, melphalan, and prednisone, followed by lenalidomide maintenance, improves health-related quality of life in newly diagnosed multiple myeloma patients aged 65 years or older: results of a randomized phase III trial. Haematologica. 2013;98(5):784–8.
43. Dimopoulos MA, Palumbo A, Hajek R, Kropff M, Petrucci MT, Lewis P, et al. Factors that influence health-related quality of life in newly diagnosed patients with multiple myeloma aged >/= 65 years treated with melphalan, prednisone and lenalidomide followed by lenalidomide maintenance: results of a randomized trial. Leuk Lymphoma. 2014;55(7):1489–97.
44. Benboubker L, Dimopoulos MA, Dispenzieri A, Catalano J, Belch AR, Cavo M, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2014;371(10):906–17.
45. Lo-Coco F, Avvisati G, Vignetti M, Thiede C, Orlando SM, Iacobelli S, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med. 2013;369(2):111–21.
46. Efficace F, Mandelli F, Avvisati G, Cottone F, Ferrara F, Di Bona E, et al. Randomized phase III trial of retinoic acid and arsenic trioxide versus retinoic acid and chemotherapy in patients with acute promyelocytic leukemia: health-related quality-of-life outcomes. J Clin Oncol. 2014;32(30):3406–12.
47. Mesa RA, Schwager S, Radia D, Cheville A, Hussein K, Niblack J, et al. The Myelofibrosis Symptom Assessment Form (MFSAF): an evidence-based brief inventory to measure quality of life and symptomatic response to treatment in myelofibrosis. Leuk Res. 2009;33(9):1199–203.
48. Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med. 2012;366(9):799–807.
49. Mesa RA, Gotlib J, Gupta V, Catalano JV, Deininger MW, Shields AL, et al. Effect of ruxolitinib therapy on myelofibrosis-related symptoms and other patient-reported outcomes in COMFORT-I: a randomized, double-blind, placebo-controlled trial. J Clin Oncol. 2013;31(10):1285–92.
50. Harrison CN, Mesa RA, Kiladjian JJ, Al-Ali HK, Gisslinger H, Knoops L, et al. Health-related quality of life and symptoms in

patients with myelofibrosis treated with ruxolitinib versus best available therapy. Br J Haematol. 2013;162(2):229–39.
51. Cervantes F, Vannucchi AM, Kiladjian JJ, Al-Ali HK, Sirulnik A, Stalbovskaya V, et al. Three-year efficacy, safety, and survival findings from COMFORT-II, a phase 3 study comparing ruxolitinib with best available therapy for myelofibrosis. Blood. 2013;122(25):4047–53.
52. Deisseroth A, Kaminskas E, Grillo J, Chen W, Saber H, Lu HL, et al. U.S. Food and Drug Administration approval: ruxolitinib for the treatment of patients with intermediate and high-risk myelofibrosis. Clin Cancer Res. 2012;18(12):3212–7.
53.• Basch E. Toward patient-centered drug development in oncology. N Engl J Med. 2013;369(5):397–400. **Highlighting the role and need for PRO in cancer drug development today**.
54. Ma X. Epidemiology of myelodysplastic syndromes. Am J Med. 2012;125(7 Suppl):S2–5.
55. Caocci G, La Nasa G, Efficace F. Health-related quality of life and symptom assessment in patients with myelodysplastic syndromes. Expert Rev Hematol. 2009;2(1):69–80.
56. Stasi R, Abruzzese E, Lanzetta G, Terzoli E, Amadori S. Darbepoetin alfa for the treatment of anemic patients with low- and intermediate-1-risk myelodysplastic syndromes. Ann Oncol. 2005;16(12):1921–7.
57. Silverman LR, Demakos EP, Peterson BL, Kornblith AB, Holland JC, Odchimar-Reissig R, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. J Clin Oncol. 2002;20(10):2429–40.
58. Kornblith AB, Herndon JE,2nd, Silverman LR, Demakos EP, Odchimar-Reissig R, Holland JF, et al. Impact of azacytidine on the quality of life of patients with myelodysplastic syndrome treated in a randomized phase III trial: a Cancer and Leukemia Group B study. J Clin Oncol. 2002 May 15;20(10):2441–52.
59. Kantarjian H, Issa JP, Rosenfeld CS, Bennett JM, Albitar M, DiPersio J, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. Cancer. 2006;106(8):1794–803.
60. Lubbert M, Suciu S, Baila L, Ruter BH, Platzbecker U, Giagounidis A, et al. Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. J Clin Oncol. 2011;29(15):1987–96.
61. Abel GA, Efficace F, Tinsley S, J, J.G., Martins Y, Steensma DP, et al. Preliminary International Validation of the Quality of Life in Myelodysplasia Scale (QUALMS). 56th Annual ASH Meeting and Exposition; December 6–9, 2014; San Francisco, CA.; 2014.
62. Abel GA, Klaassen R, Lee SJ, Young NL, Cannella L, Steensma DP, et al. Patient-reported outcomes for the myelodysplastic syndromes: a new MDS-specific measure of quality of life. Blood. 2014;123(3):451–2.
63. Gotay CC, Kawamoto CT, Bottomley A, Efficace F. The prognostic significance of patient-reported outcomes in cancer clinical trials. J Clin Oncol. 2008;26(8):1355–63.
64. Wood W, Le-Rademacher J, Fei M, Logan B, Syrjala K, Majhail N, et al. Patient-Reported Quality of Life Is an Independent Predictor of Survival after Allogeneic Hematopoietic Cell Transplantation: A Secondary Analysis from the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0902. 56th ASH Annual Meeting and Exposition; December 6–9, 2014; San Francisco, California.; 2014.
65. Thompson C, Maurer M, Allmer C, Slager S, Yost K, Macon W, et al. Quality of Life at Diagnosis Independently Predicts Survival in Patients with Aggressive Lymphoma. 56th ASH Annual Meeting and Exposition; December 6–9, @014; San Francisco, California.; 2014.
66. Sjoberg J, Halthur C, Kristinsson SY, Landgren O, Nygell UA, Dickman PW, et al. Progress in Hodgkin lymphoma: a population-based study on patients diagnosed in Sweden from 1973–2009. Blood. 2012;119(4):990–6.
67. Bouliotis G, Bessell EM. Hodgkin disease (1973–2002): long-term survival and cure fractions. Leuk Lymphoma. 2014;9:1–8.
68. Ganz PA, Moinpour CM, Pauler DK, Kornblith AB, Gaynor ER, Balcerzak SP, et al. Health status and quality of life in patients with early-stage Hodgkin's disease treated on Southwest Oncology Group Study 9133. J Clin Oncol. 2003;21(18):3512–9.
69. van Tulder MW, Aaronson NK, Bruning PF. The quality of life of long-term survivors of Hodgkin's disease. Ann Oncol. 1994;5(2):153–8.
70. Greaves P, Sarker SJ, Chowdhury K, Johnson R, Matthews J, Matthews R, et al. Fertility and sexual function in long-term survivors of haematological malignancy: using patient-reported outcome measures to assess a neglected area of need in the late effects clinic. Br J Haematol. 2014;164(4):526–35.
71. Leunis A, Redekop WK, Uyl-de Groot CA, Lowenberg B. Impaired health-related quality of life in acute myeloid leukemia survivors: a single-center study. Eur J Haematol. 2014;93(3):198–206.
72. Langeveld NE, Stam H, Grootenhuis MA, Last BF. Quality of life in young adult survivors of childhood cancer. Support Care Cancer. 2002;10(8):579–600.
73. Reed SD, Anstrom KJ, Ludmer JA, Glendenning GA, Schulman KA. Cost-effectiveness of imatinib versus interferon-alpha plus low-dose cytarabine for patients with newly diagnosed chronic-phase chronic myeloid leukemia. Cancer. 2004;101(11):2574–83.
74. Hornberger J, Rickert J, Dhawan R, Liwing J, Aschan J, Lothgren M. The cost-effectiveness of bortezomib in relapsed/refractory multiple myeloma: Swedish perspective. Eur J Haematol. 2010;85(6):484–91.
75. Zafar SY, Abernethy AP. Financial toxicity, Part I: a new name for a growing problem. Oncology (Williston Park). 2013 Feb;27(2):80,1, 149.
76. de Souza JA, Yap BJ, Hlubocky FJ, Wroblewski K, Ratain MJ, Cella D, et al. The development of a financial toxicity patient-reported outcome in cancer: the COST measure. Cancer. 2014;120(20):3245–53.
77. Sorror M, Storer B, Sandmaier BM, Maloney DG, Chauncey TR, Langston A, et al. Hematopoietic cell transplantation-comorbidity index and Karnofsky performance status are independent predictors of morbidity and mortality after allogeneic nonmyeloablative hematopoietic cell transplantation. Cancer. 2008;112(9):1992–2001.
78. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005;106(8):2912–9.
79. Gratwohl A. The EBMT risk score. Bone Marrow Transplant. 2012;47(6):749–56.
80. Broderick JM, Hussey J, Kennedy MJ, O'Donnell DM. Patients over 65 years are assigned lower ECOG PS scores than younger patients, although objectively measured physical activity is no different. J Geriatr Oncol. 2014;5(1):49–56.
81. Wood WA, Deal AM, Reeve BB, Abernethy AP, Basch E, Mitchell SA, et al. Cardiopulmonary fitness in patients undergoing hematopoietic SCT: a pilot study. Bone Marrow Transplant. 2013;48(10):1342–9.
82. Kelsey CR, Scott JM, Lane A, Schwitzer E, West MJ, Thomas S, et al. Cardiopulmonary exercise testing prior to myeloablative allo-SCT: a feasibility study. Bone Marrow Transplant. 2014;49(10):1330–6.

83. Broderick JM, Ryan J, O'Donnell DM, Hussey J. A guide to assessing physical activity using accelerometry in cancer patients. Support Care Cancer. 2014;22(4):1121–30.
84. Takacs J, Pollock CL, Guenther JR, Bahar M, Napier C, Hunt MA. Validation of the Fitbit One activity monitor device during treadmill walking. J Sci Med Sport. 2014;17(5):496–500.
85. Adam Noah J, Spierer DK, Gu J, Bronner S. Comparison of steps and energy expenditure assessment in adults of Fitbit Tracker and Ultra to the Actical and indirect calorimetry. J Med Eng Technol. 2013;37(7):456–62.
86. Lee PH, Nan H, Yu YY, McDowell I, Leung GM, Lam TH. For non-exercising people, the number of steps walked is more strongly associated with health than time spent walking. J Sci Med Sport. 2013;16(3):227–30.
87. Jim HS, Evans B, Jeong JM, Gonzalez BD, Johnston L, Nelson AM, et al. Sleep disruption in hematopoietic cell transplantation recipients: prevalence, severity, and clinical management. Biol Blood Marrow Transplant. 2014;20(10):1465–84.
88. Rischer J, Scherwath A, Zander AR, Koch U, Schulz-Kindermann F. Sleep disturbances and emotional distress in the acute course of hematopoietic stem cell transplantation. Bone Marrow Transplant. 2009;44(2):121–8.
89. Nelson AM, Coe CL, Juckett MB, Rumble ME, Rathouz PJ, Hematti P, et al. Sleep quality following hematopoietic stem cell transplantation: longitudinal trajectories and biobehavioral correlates. Bone Marrow Transplant. 2014;49(11):1405–11.
90. Weiss AR, Johnson NL, Berger NA, Redline S. Validity of activity-based devices to estimate sleep. J Clin Sleep Med. 2010;6(4):336–42.
91. Wang XS, Shi Q, Shah ND, Heijnen CJ, Cohen EN, Reuben JM, et al. Inflammatory markers and development of symptom burden in patients with multiple myeloma during autologous stem cell transplantation. Clin Cancer Res. 2014;20(5):1366–74.
92. Hjermstad MJ, Knobel H, Brinch L, Fayers PM, Loge JH, Holte H, et al. A prospective study of health-related quality of life, fatigue, anxiety and depression 3–5 years after stem cell transplantation. Bone Marrow Transplant. 2004;34(3):257–66.
93. Pallua S, Giesinger J, Oberguggenberger A, Kemmler G, Nachbaur D, Clausen J, et al. Impact of GvHD on quality of life in long-term survivors of haematopoietic transplantation. Bone Marrow Transplant. 2010;45(10):1534–9.
94. Keogh F, O'Riordan J, McNamara C, Duggan C, McCann SR. Psychosocial adaptation of patients and families following bone marrow transplantation: a prospective, longitudinal study. Bone Marrow Transplant. 1998;22(9):905–11.
95. Kopp M, Holzner B, Meraner V, Sperner-Unterweger B, Kemmler G, Nguyen-Van-Tam DP, et al. Quality of life in adult hematopoietic cell transplant patients at least 5 yr after treatment: a comparison with healthy controls. Eur J Haematol. 2005;74(4):304–8.
96. Gifford G, Sim J, Horne A, Ma D. Health status, late effects and long-term survivorship of allogeneic bone marrow transplantation: a retrospective study. Intern Med J. 2014;44(2):139–47.
97. Sarkar S, Scherwath A, Schirmer L, Schulz-Kindermann F, Neumann K, Kruse M, et al. Fear of recurrence and its impact on quality of life in patients with hematological cancers in the course of allogeneic hematopoietic SCT. Bone Marrow Transplant. 2014;49(9):1217–22.
98. Amin EN, Phillips GS, Elder P, Jaglowski S, Devine SM, Wood KL. Health-related quality of life in patients who develop bronchiolitis obliterans syndrome following allo-SCT. Bone Marrow Transplant. 2014 Nov 24.
99. Wood WA, Deal AM, Abernethy A, Basch E, Battaglini C, Kim YH, et al. Feasibility of frequent patient-reported outcome surveillance in patients undergoing hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2013;19(3):450–9.
100. Jensen RE, Snyder CF, Abernethy AP, Basch E, Potosky AL, Roberts AC, et al. Review of electronic patient-reported outcomes systems used in cancer clinical care. J Oncol Pract. 2014;10(4):e215–22.
101. Basch EM, Reeve BB, Mitchell SA, Clauser SB, Minasian L, Sit L, et al. Electronic toxicity monitoring and patient-reported outcomes. Cancer J. 2011;17(4):231–4.
102. Moore HK, Santibanez ME, Denzen EM, Carr DW, Murphy EA. Barriers to accessing health care for hematopoietic cell transplantation recipients living in rural areas: perspectives from healthcare providers. Clin J Oncol Nurs. 2013;17(4):405–11.