bjh review

Health-related quality of life following haematopoietic cell transplantation: patient education, evaluation and intervention

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Summary

Health-related quality of life (QOL) is a vital concern in the pre-treatment consent process and post-treatment care of recipients of haematopoietic cell transplantation (HCT). We propose that comprehensive care of such patients requires an integration of knowledge of the impact of HCT on QOL, assessment of QOL, as well as resources available for intervention. This knowledge may significantly improve patient care when incorporated into daily clinical practice in the transplant setting. As a framework for this approach, this article reviews the literature on QOL after allogeneic and autologous HCT for adults with haematological malignancies. We then discuss evidence in support of the beneficial impact of clinical QOL assessment, and finally evaluate behavioural interventions that show promise to maintain or improve QOL after HCT.

Keywords: quality of life, bone marrow transplant module, cancer, stem cell transplantation.

Advances in haematopoietic cell transplantation (HCT) have allowed expanded access, reduction in transplant-related morbidity and mortality, and improved long-term outcomes. However, this intensive therapy still entails a significant burden of associated short- and long-term morbidity (Curtis *et al*, 1997; Duell *et al*, 1997; Lee *et al*, 2004; Gratwohl *et al*, 2006) with potential threats to health-related quality of life (QOL). In recognition of the central role of QOL in cancer treatment, the American Society of Clinical Oncology (ASCO) has designated QOL second in importance only to survival (ASCO 1996, Halyard & Ferrans, 2008). Thus, an important goal of HCT is not only survival, but also maintenance of patient QOL. Because post-treatment QOL is also one of cancer patients' greatest concerns (Molassiotis & Morris, 1998; Baker *et al*, 2005; Heinonen *et al*, 2005), a proactive approach to addressing QOL is essential in the transplant setting. We argue that a comprehensive discussion of the anticipated risks, benefits, and potential threats to QOL incurred by HCT is therefore highly relevant to patients during the process of obtaining informed consent for treatment (Bush *et al*, 2005). Following HCT, ongoing evaluation of QOL with appropriate intervention is a critical aspect of clinical care, for which there is a growing evidence base. Unfortunately, the data suggest that evaluation of post-transplant QOL may be commonly overlooked by providers (Hendriks & Schouten, 2002). As such, opportunities to intervene to improve QOL may go unnoticed.

The goal of this review is to provide a comprehensive overview of current literature regarding QOL following allogeneic and autologous HCT for adults with haematological malignancies, with an emphasis on provider-patient communication about post-transplant QOL. The review begins with a definition of QOL, and then is divided into three main sections as summarized in Table I. The first section reviews current literature on QOL outcomes after HCT for adult patients with haematological malignancies to provide a conceptual framework for educating patients during the consent process about the QOL they can expect post-transplant. Evidence regarding longitudinal changes in QOL and comparisons of QOL between patients and individuals without cancer is reviewed for allogeneic and autologous transplantation and is also summarized in Table II. As a singular focus on impairment of QOL after HCT may lead to an imbalanced view, we also emphasize patient-reported benefits of HCT, including a discussion of post-traumatic growth. Caregiver QOL is also addressed as an important factor in patient recovery. The second section focuses on the importance of evaluating post-transplant QOL in the context of follow-up care. Current literature and suggestions for clinical evaluation of QOL are reviewed. The third section describes evidence for interventions to improve or maintain QOL following HCT. The review concludes with a summary and recommendations to researchers and clinicians.

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Table I. Essential skills for optimizing QOL in the continuum of care of HCT recipients.

Time	Skills
Before HCT	1) Counsel prospective patients on the impact of HCT on QOL – Focus on specific anticipated abilities and limitations – Describe positive outcomes and opportunity for personal growth
After HCT	2) Assess QOL in the clinical care of HCT patients – Identify those who are at increased risk for impaired QOL – Perform regular assessment of QOL in clinical follow up 3) Provide behavioural intervention to maintain or restore QOL after HCT – Make early referral to allied providers in multi-disciplinary team

QOL, quality of life; HCT, haematopoietic cell transplantation.

Defining QOL

The World Health Organization (WHO 1995) defines QOL as 'individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is concerned with a wide-ranging concept influenced in a rather complex fashion by the physical health of the subject, the psychological state, his level of independence, his social relations as well as the relation the person has with the essential elements of his environment'. QOL is a dynamic, multi-dimensional construct that is most often assessed via patient self-report. In contrast to symptoms, which describe how a patient feels, QOL refers to patient functioning, or what a patient can and cannot do (Buchanan *et al*, 2007). Because symptoms impact functioning, they are often assessed as part of QOL. However, QOL is distinct from individual symptoms due to the influence of social and psychological factors on QOL. While domains of QOL vary somewhat by the assessment instrument used, there is general consensus that QOL encompasses physical functioning, emotional functioning, social functioning, role functioning, and overall QOL. Physical

Table II. Summary of current research on QOL in allogeneic and autologous HCT patients.

QOL domain	Allogeneic HCT	Autologous HCT
Physical functioning	Lower than population norms prior to HCT Nadirs at 30–100 days Improvement to pre-HCT levels after 1 year Continued long-term impairment relative to non-cancer comparison groups	Lower than population norms prior to HCT Nadirs at 10 days to 6 weeks Improvement to pre-HCT levels or beyond after 3 months Continuing long-term impairments
Emotional functioning	High levels of distress prior to and after HCT Small improvements by day 100 Stable or improved functioning through years 2–4 Continued long-term impairment relative to non-cancer comparison groups	Impairment from baseline up to 1 month after HCT Return to baseline by 3–6 months
Social functioning	Lower than population norms prior to HCT Nadir values 90–100 days post-HCT Return to baseline functioning by 1 year Continued long-term impairment relative to non-cancer comparison groups	Baseline comparable or better than controls Nadir by 1 month Return to baseline by 3–6 months
Role functioning	Lower than population norms prior to HCT Nadir throughout first 100 days Return to baseline by 1 year, followed by ongoing improvement Continued long-term impairment relative to non-cancer comparison groups	Lower than population norms prior to HCT Early nadir reported at 10 days post-HCT Return toward baseline from 90 days to 1 year post-HCT Continued long-term impairment relative to non-cancer comparison groups
Overall QOL	Baseline comparable to population norms prior to HCT Nadir by day 30 Return to baseline by day 100 Ongoing improvements reported from 6 months to 4 years post-HCT Continued long-term impairment relative to non-cancer comparison groups	Lower than population norms prior to HCT Nadir 10–14 days after HCT Return to baseline by 3 months to 1 year Continued long-term impairment relative to non-cancer comparison groups

QOL, quality of life; HCT, haematopoietic cell transplantation.

functioning refers to how a person assesses the impact of physical health on their normal daily activities, such as difficulty with self-care, time spent in bed, and ability to engage in activities such as walking or climbing one or more flights of stairs. Across QOL instruments, subjects are commonly asked to characterize the impact on functioning of fatigue, pain, difficulty breathing, nausea, and specific side effects from treatment. Emotional functioning refers to overall mood, distress, anxiety, fears related to diagnosis and treatment, and overall degree of hope. Social functioning indicates a person's ability to engage in their normal social interactions, relationships, and family dynamics (Bush *et al*, 1995). Patients are typically asked to rate their relationships with friends and family, as well as their satisfaction with communication and support within important relationships. Role functioning indicates how well survivors are able to perform their usual roles in the home, work, school and community, and how their symptoms interfere with these roles. Finally, overall QOL reflects the patients' comprehensive assessment of their functioning in all domains of life.

QOL after HCT

Physical functioning

Allogeneic HCT. Prior to transplant, patients' physical functioning is significantly lower than population norms (Hjermstad *et al*, 2004), potentially due to previous induction chemotherapy as well as residual symptoms of disease. As may be anticipated by the rigours of the transplant process, patients suffer a decline in their physical functioning immediately after HCT, with nadir values reported from 30 to 100 days post-HCT (Syrjala *et al*, 1993; McQuellon *et al*, 1998; Lee *et al*, 2004; Altmaier *et al*, 2006; Bevans *et al*, 2006; Schulz-Kindermann *et al*, 2007). Following this nadir, several studies demonstrated improvement with either a plateau in the first year (Lee *et al*, 2004; Bevans *et al*, 2006) or ongoing improvement over 4 years following HCT (Bush *et al*, 2000). For example, between day 100 and 1 year after HCT, the proportion of patients endorsing the statement 'I have a lack of energy' decreased from 64% to 51% and the proportion of patients endorsing 'I am bothered by side effects of treatment' decreased from 32% to 22% (McQuellon *et al*, 1998). Impaired physical recovery at 1 year is predicted by more severe chronic graft-versus-host disease (GVHD), pre-transplant physical impairment and family conflict (Syrjala *et al*, 1993; Worel *et al*, 2002). Ongoing bothersome symptoms in HCT survivors at 24 months post-HCT include the following: pain 11%; mouth sores 9%; painful joints 20%; skin changes 16%; fatigue 33%; sexual difficulties 36% (Lee *et al*, 2001). Similarly, 25% of long-term transplant survivors display ongoing significant medical problems at an average of 42 months (Wolcott *et al*, 1986). The physical complaints most commonly endorsed by these survivors included mouth soreness, nausea, abdominal cramps, diarrhoea, and skin itching (Wolcott *et al*, 1986). At an average of 42 months post-HCT 33% of respondents reported frequent infections, 35% reported emergency room visits, 46% reported frequent physician visits, and 15% reported one or more hospitalizations in the preceding year (Wolcott *et al*, 1986). In addition, Syrjala *et al* (2004) reported that 5 years after HCT, 18% of patients experience major limitations in physical functioning, a decrease from 25% before HCT. At 5–10 years post-transplant, when recovery is expected to be complete, transplant survivors still evidence small to moderate physical impairments relative to individuals without cancer (Kiss *et al*, 2002; Andrykowski *et al*, 2005; Kopp *et al*, 2005). Therefore, while ongoing physical limitations persist, many patients will experience recovery in physical functioning after HCT to levels similar to that before transplantation and lower than individuals without cancer.

Autologous HCT. The trajectory of physical functioning after autologous transplantation is similarly one of progressive recovery following an initial decline. In a sample of multiple myeloma patients prior to transplant, physical functioning was impaired in comparison to a reference healthy population, notably consisting of pain, fatigue, and appetite loss (Gulbrandsen *et al*, 2004). Following autologous HCT, several longitudinal series have demonstrated initial worsening compared to baseline values, with a nadir variably reported at 10–14 days (van Agthoven *et al*, 2001; Vellenga *et al*, 2001; Sherman *et al*, 2009) to 4–6 weeks (Schulmeister *et al*, 2005) after HCT. These deficits are probably due to the acute effects of the conditioning regimen, including nausea, vomiting, and mucositis (Chao *et al*, 1992). Moving forward, studies demonstrate progressive improvement returning to or surpassing baseline values by 3 months (van Agthoven *et al*, 2001), 6 months (Schulmeister *et al*, 2005), or 1 year (Chao *et al*, 1992; Gulbrandsen *et al*, 2004). In one study, at 1 year post-autologous HCT 53% reported stable weight, 88% reported appetite as good, only 5% reported difficulty sleeping, and 64% reported sexual functioning as satisfying as compared to pre-transplant (Chao *et al*, 1992). Similarly, the proportion below the 10^{th} percentile of physical functioning in a normative population decreased from 67% at baseline to 48% by 1 year (Gulbrandsen *et al*, 2004). At 36 months post-autologous HCT, there appear to be ongoing impairments: greater than 60% of patients reported difficulty with strenuous activities (e.g. carrying a shopping bag), and up to 70% reported difficulty taking a long walk (Gulbrandsen *et al*, 2004). This degree of impairment is somewhat surprising 3 years after autologous HCT, and may in part be explained by additional factors including poor baseline functioning as well as age, as evidenced by a greater proportion reporting these difficulties in the age >60 years subgroup from this report. Long-term physical functioning may also be compromised by relapsed disease after autologous HCT.

Emotional functioning

Allogeneic HCT. As may be expected, given the uncertainty, fears, and anticipated difficulties of transplantation, the period immediately before transplant is highly stressful, with significant distress, anxiety, and uncertainty (Hjermstad *et al*, 1999a). Similarly, the acute transplant period is also emotionally difficult. Patients report high levels of distress during this time (McQuellon *et al*, 1998; Bevans *et al*, 2006). Small improvements are seen by day 100 (Syrjala *et al*, 1993; Bevans *et al*, 2006; Schulz-Kindermann *et al*, 2007). Nevertheless, McQuellon *et al* (1998) found that 43% of HCT recipients reported depressive symptoms at one or more points through the first year after HCT. Predictors of greater emotional distress include female gender (Heinonen *et al*, 2001), pre-HCT family conflict (Syrjala *et al*, 1993), non-married status (Syrjala *et al*, 1993), and development of less severe chronic GVHD (Syrjala *et al*, 1993). It has been speculated that the negative relationship between severity of GVHD and emotional distress occurs because patients with more severe GVHD are focused more on medical problems than emotional concerns (Syrjala *et al*, 1993). Further research is needed on the relationship between GVHD severity and distress. Moving forward after transplant, there are conflicting results, with some studies indicating stable findings at time points thereafter (Syrjala *et al*, 1993; McQuellon *et al*, 1998), and others demonstrating ongoing improvement through years 2–4 after HCT (Syrjala *et al*, 1993; McQuellon *et al*, 1998; Bush *et al*, 2000; Bevans *et al*, 2006; Schulz-Kindermann *et al*, 2007). In long-term follow up, more persistent impairments in emotional functioning are suggested: 15-25% of HCT survivors at an average of 42 months after HCT reported ongoing emotional distress, low self-esteem, and low life satisfaction (Wolcott *et al*, 1986). Other studies support significant impairments in emotional functioning in HCT survivors compared to healthy controls at 5–10 years after HCT (Hjermstad *et al*, 1999b; Andrykowski *et al*, 2005; Kopp *et al*, 2005; Syrjala *et al*, 2005). While the overall trend in longitudinal recovery is encouraging, those with persistent difficulty in emotional functioning will require appropriate referral for support and counselling.

Autologous HCT. Similar to early impairments reported after allogeneic HCT, recipients of autologous HCT endure early challenges in emotional functioning that are probably due to anticipatory anxiety related to the transplant. Anxiety and depression are present in up to 40% of autologous patients at the time of stem cell collection prior to HCT (Sherman *et al*, 2009). By 10 days after HCT, the prevalence is 48%, with patients reporting trouble with depression and overall life satisfaction (Sherman *et al*, 2009). Similarly, greater impairment in emotional functioning is observed 1 month after autologous HCT compared to baseline (Schulmeister *et al*, 2005). However, progressive improvements are thereafter reported either reaching or surpassing baseline emotional functioning by 3–6 months after autologous HCT (van Agthoven *et al*, 2001; Schulmeister *et al*, 2005). Unfortunately, longer term data regarding emotional functioning are lacking in survivors of autologous HCT.

Social functioning

Allogeneic HCT. Significant impairments in social functioning are present relative to population norms even before transplant (Hjermstad *et al*, 2004). As assessed by longitudinal measures of QOL, small to moderate impairments in social functioning are also seen after allogeneic transplant, with nadir values described from 90 to 100 days post-HCT (Syrjala *et al*, 1993; Schulz-Kindermann *et al*, 2007). Encouragingly, however, social functioning improves thereafter, with transplant survivors reporting social functioning that is similar to or better than baseline by 1 year post-HCT (Syrjala *et al*, 1993; McQuellon *et al*, 1998; Hjermstad *et al*, 1999b). As described by Lee *et al* (2001), long-term recovery of social functioning is good, with 84% of survivors enjoying socializing with family and friends by 2 years, a progressive improvement from 52% at 6 months, and 77% at 1 year. Even further improvements are observed by 3 to 4 years post allogeneic HCT (Bush *et al*, 2000; Gulbrandsen *et al*, 2004). GVHD is an important predictor of impaired social functioning (Chiodi *et al*, 2000; Worel *et al*, 2002). In comparison with healthy controls and population normative data at 5–10 years after HCT, there are persistent, but small to moderate decrements in social functioning (Sutherland *et al*, 1997; Kopp *et al*, 2005). Thus, while survivors treated with allogeneic transplant show significant improvements in social functioning over time, enduring impairments are nevertheless observed relative to individuals without cancer.

Autologous HCT. After autologous HCT, there is again an overall trend of progressive improvements in social functioning. Interestingly, Sherman *et al* (2009) reported that multiple myeloma patients prior to autologous HCT actually reported significantly better social well being than both healthy control subjects and in comparison with a non-myeloma autologous HCT reference group; the authors suggest that, while the reasons for this are unclear, it may reflect the supports provided by the patient's caregiver and psychosocial support services available to them (Sherman *et al*, 2009). However, other data indicate impairments in social functioning before transplant relative to population norms (Hjermstad *et al*, 2004). Evidence for decreased social functioning immediately post-transplant is similarly mixed, with one study reporting minimal changes in social functioning from baseline to 10 days after HCT (Sherman *et al*, 2009) and another reporting decreased social functioning from baseline to 1 month post-HCT (Schulmeister *et al*, 2005). The literature supports ongoing recovery reaching or surpassing baseline levels by 3–6 months (van Agthoven *et al*, 2001; Schulmeister *et al*, 2005); however, additional data beyond this time point are lacking.

Role functioning

Allogeneic HCT. Role functioning is a topic that is of considerable interest to patients, as individuals often define themselves in relation to their roles in their family and community (Charmaz, 1983; Steeves, 1992). Of particular significance is return to paid employment, which can have important consequences on financial security. Patient's role functioning prior to allogeneic transplant is significantly lower than population norms (Hjermstad *et al*, 2004), probably due to the effects of previous treatments. Patients' roles are further circumscribed by the prolonged hospitalization necessitated by allogeneic transplant. On average, patients can expect moderate to large decreases in role functioning, work functioning, and home management in the first 100 days after transplant (Syrjala *et al*, 1993; Schulz-Kindermann *et al*, 2007). Data suggest these decreases are transient, however. By 1 year post-transplant, average role functioning has returned to baseline levels or improved slightly relative to baseline (Syrjala *et al*, 1993; Hjermstad *et al*, 1999c, 2004). Available evidence suggests that survivors can further expect continued moderate improvement in role functioning in the years following transplant (Sutherland *et al*, 1997). However, three or more years after transplant survivors are still significantly impaired relative to individuals without cancer (Kiss *et al*, 2002; Hayden *et al*, 2004; Kopp *et al*, 2005), although some data show comparable role functioning (Sutherland *et al*, 1997). Regarding return to work or school, 67% of patients surviving transplant had returned to work or school at 1 year, 80% at 2 years, 80% at 3 years, and 74% at 4 years (Bush *et al*, 2000; Lee *et al*, 2001). These rates are consistent with other data suggesting that 84% of survivors without relapse have returned to work or school at 5 years post-transplant (Syrjala *et al*, 2004). By 10 years post-transplant, survivors do not differ in rates of full-time employment from age-, race-, and sex-matched controls without cancer (72% vs. 74%, respectively) (Syrjala *et al*, 2005). Of all patients transplanted, including individuals who died or relapsed, 20% had returned to work or school by 1 year, 31% by 2 years, 33% by 3 years, and 34% by 5 years (Syrjala *et al*, 2004). Female gender and extensive chronic GVHD are associated with reduced role functioning (Chiodi *et al*, 2000; Worel *et al*, 2002; Fraser *et al*, 2006) and delayed return to work (Worel *et al*, 2002; Syrjala *et al*, 2004). In general, the majority of individuals who survive transplant and remain disease-free can expect to resume work, school and other roles in the community. Nevertheless, research has not documented the extent to which survivors must accommodate reduced health status by engaging in less demanding roles, such as part-time work.

Autologous HCT. Large deficits in role functioning have been observed in autologous patients prior to transplant compared to population norms (Gulbrandsen *et al*, 2004; Sherman *et al*, 2009), reflecting the challenges of maintaining roles while coping with the process of diagnosis and initial treatment. Indeed, role functioning is one of the domains of QOL that is most impaired prior to HCT (Gulbrandsen *et al*, 2004). Not surprisingly, deficits in role functioning are also large compared to population norms in the 10 days post-transplant (Sherman *et al*, 2009). However, autologous patients appear to improve rapidly following transplant. For example, approximately 50% of survivors are employed at 90 days post-transplant, and 78% at 1 year (Chao *et al*, 1992). Nevertheless, significant deficits in role functioning continue to be evident relative to individuals without cancer. While improvements in role functioning at 3 years post-transplant are evident compared to baseline, moderate to large deficits are still observed relative to a reference population.(Gulbrandsen *et al*, 2004) As time progresses, role functioning appears to decline again, probably due to relapse. At 5 years post-transplant, 60% of younger autologous survivors (i.e., age < 60 years) and 50% of older survivors (i.e., age 60 years or more) reported limitations in work or household activities (Byar *et al*, 2005). Predictors of decreased role functioning in autologous transplant survivors include younger age and treatment with thalidomide (Sherman *et al*, 2009). Although long-term longitudinal studies of QOL are lacking in haematological patients treated with autologous HCT, available data suggest short-term improvements in role functioning. Additional studies are needed regarding the direct effects of relapsed disease on role functioning.

Overall QOL

Allogeneic HCT. Although specific impairments in the domains of physical, social, and role functioning are observed prior to transplant in patients relative to population norms, patients typically report overall QOL at baseline that is comparable to healthy individuals (Hjermstad *et al*, 2004). Overall QOL remains stable or declines following transplant, with lowest values within 30 days (McQuellon *et al*, 1998; Bevans *et al*, 2006). Prompt improvements are then seen, with overall QOL largely returning to or surpassing baseline values by day 100 (McQuellon *et al*, 1998; Bevans *et al*, 2006; Schulz-Kindermann *et al*, 2007). Several studies have demonstrated ongoing moderate to large improvements in overall QOL compared to baseline values at assessments including 6 months (Broers *et al*, 2000; Byar *et al*, 2005), 1 year (Andrykowski *et al*, 1995; McQuellon *et al*, 1998; Broers *et al*, 2000; Heinonen *et al*, 2001; Byar *et al*, 2005; Bevans *et al*, 2006), 2 years (Heinonen *et al*, 2001; Bevans *et al*, 2006), and 3 years (Hjermstad *et al*, 1999b; Broers *et al*, 2000). Through years one to four following transplant, 73%, 76%, 81% and 80% of transplant survivors, respectively, reported their overall QOL as 'good to excellent' (Bush *et al*, 2000). Additionally, 71% agree with the statement, 'I have recovered from my transplant' by 2 years post-HCT (Lee *et al*, 2001). Interestingly, as assessed by the Functional Assessment of Cancer Therapy – Bone Marrow Transplant Module

(FACT-BMT), 93% respond 'not at all' to the statement 'I regret having the BMT' at 1 year post-HCT (McQuellon *et al*, 1998). Predictors of impaired overall QOL include GVHD, greater symptoms, lower educational level, older age, a shorter time after HCT, female gender, and impotence (Prieto *et al*, 1996; Lee *et al*, 2006). Despite longitudinal improvements in overall QOL, significant deficits are nonetheless observed when comparing survivors of allogeneic HCT to either healthy volunteers or population normative data. At 5–10 years post-HCT, decrements in overall QOL of small to moderate magnitude have been reported (Kopp *et al*, 2005). Self reported QOL is largely positive at points from 6 to 18 years post-HCT, with up to 80% reporting 'good to excellent' overall QOL, and 74% reporting QOL as 'same or better' than pre-HCT levels (Baker *et al*, 1994; Bush *et al*, 1995; Edman *et al*, 2001). These data support that early impairments largely improve, with generally good overall QOL following allogeneic HCT.

Autologous HCT. In the setting of autologous HCT, initial impairments in overall QOL are noted at baseline compared to reference population data, probably reflecting the effects of prior therapy and anticipation of the arduous therapy involved in autologous HCT (Gulbrandsen *et al*, 2004). Not surprisingly, longitudinal studies demonstrate an initial worsening in overall QOL following transplant, with nadir reached at 10–14 days after HCT (van Agthoven *et al*, 2001; Vellenga *et al*, 2001; Sherman *et al*, 2009). Beyond this, there is rapid progressive improvement, with return to baseline reported by 3 months (van Agthoven *et al*, 2001) to 1 year (Chao *et al*, 1992; Gulbrandsen *et al*, 2004). By 1 year after autologous HCT, the proportion of survivors below the 10^{th} percentile of a healthy normative population in overall QOL decreased from 43% to 20% (Gulbrandsen *et al*, 2004). In addition, 88% of survivors after autologous HCT at 1 year endorsed their overall QOL as 'above average to excellent' (Chao *et al*, 1992). However, there does appear to be a more persistent decrement in overall QOL after autologous HCT in comparison to normative population data at 36 months (Gulbrandsen *et al*, 2004). Thus, it appears that deficits in overall QOL associated with autologous transplant are transient. Longer-term deficits in overall QOL observed in patients relative to individuals without cancer may reflect the cumulative burden of relapsed disease and multiple treatments rather than specific effects of autologous transplant *per se*.

Patient-reported benefits of HCT

Importantly, the bulk of studies investigating QOL after HCT have focused on its negative impact. HCT is an intense treatment associated with numerous acute and late physical complications, threats to QOL, impairments in cognitive and psychological functioning, as well as impact on important roles and relationships. However, a singular focus on these negative consequences leads to a biassed impression, which ignores the potential positive impact on psychological and interpersonal growth, or post-traumatic growth (Andrykowski *et al*, 1993, 2005; Fromm *et al*, 1996; Widows *et al*, 2005; Bishop *et al*, 2007; Wettergren *et al*, 2008). Tedeschi and Calhoun (2004) defined posttraumatic growth as the 'positive psychological change experienced as a result of the struggle with highly challenging life circumstances'. It represents something new and positive that is believed to surpass what was present before the trauma (Tedeschi & Calhoun, 2004). Also known as benefit-finding (Stanton *et al*, 2002; Sears *et al*, 2003; Tomich & Helgeson, 2004) or stress-related growth (Park *et al*, 1996), it refers to the reinterpretation of traumatic life events as an opportunity for personal growth. This is based on the recognition that a traumatic event can induce both positive and negative consequences. In this way, HCT is theorized to serve as the trauma or stressor that induces this adaptation and growth. Indeed, HCT survivors have reported positive outcomes including an enhanced appreciation for life, love and appreciation for family and friends, different priorities, and greater religious or spiritual beliefs (Andrykowski *et al*, 2005; Widows *et al*, 2005; Wettergren *et al*, 2008). For example, data indicate that 59% of HCT survivors reported a new philosophy on life, 47% described having a greater appreciation of life, 71% had made changes in personal characteristics or attributes, and 52% experienced improved relationships with family (Fromm *et al*, 1996). Interestingly, those who had a poorer prognosis at HCT reported greater benefits of HCT. The authors postulate that the burden and threat of their tenuous prognosis served as a more potent catalyst of growth (Fromm *et al*, 1996). Perceived benefits of HCT did not correlate with the indices of QOL and psychosocial adjustment, which raises questions about the ability of commonly used QOL indices to capture positive consequences from HCT (Fromm *et al*, 1996). This finding in particular highlights the relevance of utilizing specific instruments developed to assess post-traumatic growth for this purpose. Moreover, findings on patient-reported benefits of HCT suggest a psychological mechanism by which HCT survivors may adapt to the ongoing health challenges they face following transplant.

QOL in caregivers of HCT patients

There has been disproportionately little attention paid to the partners and caregivers of the recipients of HCT. The exception is a study of 177 HCT survivor/partner pairs and 133 healthy controls at a median of 6·7 years after HCT (Bishop *et al*, 2007). This study explored this issue by examining QOL and post-traumatic growth in HCT survivors' partners, HCT survivors, and healthy controls. While the partners of HCT survivors had comparable physical health to controls, they had significantly increased fatigue, cognitive dysfunction, depressive symptoms, sexual problems and less sleep than the controls. They also reported significantly less social support and spiritual well being, as well as more loneliness compared to both the HCT survivors and controls.

Unfortunately, partners suffered these adverse effects, but did not achieve levels of post-traumatic growth beyond that seen in the control subjects. This important work draws attention to a potentially vulnerable, yet integral, component of the successful recovery of the HCT survivor. It is important to discuss resources available to caregivers, such as respite care or support groups, within the context of a multi-disciplinary team caring for HCT patients.

Clinical evaluation of QOL

Clinical evaluation of post-transplant QOL provides an important opportunity to detect and address deficits in physical and psychosocial functioning that might otherwise be overlooked, thus improving patient care. While there is a growing body of research examining the clinical utility of QOL assessment, there have been few studies to date examining this issue specifically in the context of HCT. Nevertheless, data from oncology samples suggest that while oncologists are interested in integrating QOL questionnaires into their practice, few have done so yet (Bezjak *et al*, 2001). Instead, the majority of oncologists rely on informal assessment of QOL, such as through clinical judgment or the expectation that patients will report QOL problems (Bezjak *et al*, 2001). However, data suggest that patients do not always report QOL problems during the clinical visit (Velikova *et al*, 2008). Moreover, proxy evaluation of QOL is often not accurate. For example, compared to patients and their partners, physicians tend to underestimate symptoms and overestimate patients' QOL (Hendriks & Schouten, 2002).

Standardized evaluation of QOL and incorporation of QOL data in routine clinical practice is gaining increased attention as an alternative to reliance on physician judgment and patient reports (Halyard & Ferrans, 2008). Indeed, it has been suggested that collection of QOL data is analogous to collection of other types of medical data (e.g., laboratory and radiographic results) to obtain a complete clinical picture (Halyard *et al*, 2006; Halyard & Ferrans, 2008). Randomized clinical trials have examined the effects of clinical assessment of QOL on patient outcomes (McLachlan *et al*, 2001; Detmar *et al*, 2002; Velikova *et al*, 2004). In these trials, patients have typically completed the QOL assessment via paper-and-pencil or computerized tablet while waiting for their appointment. A graphic summary profile of patient QOL and symptoms, including comparisons to previous visits, is then printed and given to the physician and/or patient. Evidence suggests that this practice improves patient outcomes with minimal burden on patients or clinical staff. For example, a randomized controlled trial demonstrated that clinical assessment of QOL resulted in improved physician knowledge of patients' functional abilities, increased patient-physician communication regarding QOL, greater physician counselling regarding management of health problems, improved patient QOL in emotional and role functioning, and greater patient satisfaction (Detmar *et al*, 2002). There were no differences in the duration of patient visits between intervention and control arms. Additional randomized controlled trials suggest that clinical assessment of QOL results in improved patient QOL (Velikova *et al*, 2004), decreased depression in moderately to severely depressed patients (McLachlan *et al*, 2001), and better patient-physician communication regarding QOL (Velikova *et al*, 2004) without increasing the duration of visits (Velikova *et al*, 2004). Moreover, clinical assessment of QOL has high acceptability to both patients and physicians (McLachlan *et al*, 2001; Detmar *et al*, 2002; Velikova *et al*, 2004), findings which have been corroborated by other, non-randomized studies (Buxton *et al*, 1998; Velikova *et al*, 1999; Taenzer *et al*, 2000; Wright *et al*, 2003). Further research is now needed specifically within transplant settings.

A variety of measures have been developed to assess QOL that are appropriate for both research and clinical settings. These include measures of general QOL that are appropriate for both patients and non-patient comparison groups [e.g., Medical Outcomes Study – Short Form 36, MOS SF-36 (Ware *et al*, 1993)], measures designed to assess QOL specifically in cancer patients [e.g., Cancer Rehabilitation Evaluation System – Short Form, CARES-SF (Schag *et al*, 1990); European Organization for the Research and Treatment of Cancer QOL Questionnaire, EORTC QLQ-C30 (Aaronson *et al*, 1993); Functional Assessment of Cancer Therapy – General, FACT-G (Cella *et al*, 1993)], and measures designed to assess QOL specifically in HCT patients [e.g., FACT-BMT (McQuellon *et al*, 1997); City of Hope/Stanford Longterm BMT Survivor Index, COH-QOL (Schmidt *et al*, 1993)]. All of the above measures are well-validated and have been used to assess QOL specifically in HCT patients. These measures are typically short, with minimal patient burden. Thus, all would be appropriate for use in the clinical setting.

Nevertheless, one potential barrier to standardized clinical assessment of QOL is logistics. Physicians may be concerned about the initial expense of materials such as computerized tablets and software to collect and analyse QOL data. As noted by Wright *et al* (2003), 'The collection of QOL data should become robust, inexpensive, easy and readily interpretable'. They note that the ideal is for patients to complete standardized, reliable, validated self-report QOL measures (Wright *et al*, 2003). The data would then be analysed, scored, and presented to clinicians in real time. Additional suggestions have been to map QOL outcomes to standardized toxicity grading and to allow patients to check which aspects of QOL they would like to discuss with clinical staff (Velikova *et al*, 2008). To this end, several automated systems for assessing QOL have been developed by researchers for clinical use (Middeke *et al*, 2004; Velikova *et al*, 1999; http://www.nihpromis.org/default.aspx), which could easily be adapted to transplant settings. An additional option is Internet-based assessment, in which patients can complete the QOL measures over the Internet, either from home or in the waiting room (Basch *et al*, 2005; Jones *et al*, 2007; Snyder *et al*, 2009). Patients can then print out a summary to bring to their clinical

visit or results can be downloaded into a portable electronic medical records format (Jones *et al*, 2007). Some Internet-based software also provides assessment of toxicity using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) (Basch *et al*, 2005). Internet-based QOL assessment has been pilot tested in the context of HCT and shows high patient feasibility and acceptability (Bush *et al*, 2005). Thus, for oncologists wishing to incorporate assessment of QOL into their clinical practice, a variety of tools are available or under development.

Behavioural interventions to improve QOL

For HCT patients who report deficits in functioning, proactive pharmacologic symptom management may have beneficial effects on QOL. Behavioural interventions, including exercise and psychosocial interventions, also show promise in improving QOL following HCT. Regarding exercise, supervised programmes for hospitalized transplant patients have been tested in four randomized controlled trials (Dimeo *et al*, 1997; Mello *et al*, 2003; DeFor *et al*, 2007; Baumann *et al*, 2009). An additional randomized controlled trial examined a home-based exercise programme in combination with epoetin alfa in outpatients undergoing autologous transplant (Coleman *et al*, 2008). Interventions consisted of aerobic exercise (Dimeo *et al*, 1997; DeFor *et al*, 2007) or aerobic exercise in combination with strength training and stretching (Mello *et al*, 2003; Coleman *et al*, 2008; Baumann *et al*, 2009). The trials showed several benefits of exercise, including maintenance of muscle strength (Mello *et al*, 2003; Baumann *et al*, 2009) and physical performance (Dimeo *et al*, 1997; DeFor *et al*, 2007), reduced red blood cell and platelet transfusions (Coleman *et al*, 2008), and improvements in lung functioning (Baumann *et al*, 2009), physical endurance (Baumann *et al*, 2009), overall QOL (Baumann *et al*, 2009), and self-reported physical functioning (DeFor *et al*, 2007; Baumann *et al*, 2009). In all four inpatient studies, study staff visited patients in their hospital rooms several times a week to improve adherence. Exercise was generally well-tolerated during the hospitalization period, with 68% of the treatment group reporting exercise 5 times a week or more (DeFor *et al*, 2007). Further, patients reported the following benefits of exercise: improved strength and energy, alleviation of boredom, increased endurance, maintenance of flexibility, and emotional distraction (DeFor *et al*, 2007). Additional studies have examined the effects of exercise programmes in HCT survivors. These studies have used single-group, non-randomized designs and have focused on supervised (Dimeo *et al*, 1996; Carlson *et al*, 2006) (Dimeo *et al*, 1997; Hayes *et al*, 2004) or home-based aerobic exercise (Wilson *et al*, 2005). All studies reported improvements following the intervention, including decreased fatigue (Wilson *et al*, 2005; Carlson *et al*, 2006), increased physical well-being (Wilson *et al*, 2005), increased overall QOL (Hayes *et al*, 2004), and increased aerobic fitness (Dimeo *et al*, 1996, 1997; Wilson *et al*, 2005; Carlson *et al*, 2006). One study noted that improvements in fatigue were maintained 1 year after the intervention, indicating that the beneficial effects of an exercise programme may be sustained (Carlson *et al*, 2006).

Psychosocial interventions also show promise in improving outcomes in HCT. Psychosocial interventions in HCT have been examined in two randomized controlled trials (Syrjala *et al*, 1992, 1995). Neither examined QOL as an outcome but were instead designed to test the effects of stress management and cognitive-behavioural skills training on pain, nausea, and emesis compared to usual care and a time and attention control. Stress management consisted of individual training in progressive muscle relaxation (i.e., tensing and relaxing each major muscle group) and guided imagery related to relaxation and improved health. Cognitive-behavioural skills added positive self-statements, distraction, and goal setting to stress management training. Patients received two 90-min sessions prior to transplant and ten 30-min booster sessions during hospitalization. In both trials, patients in the stress management and coping skills groups reported reduced pain (Syrjala *et al*, 1992, 1995). Coping skills training did not appear to enhance the effects of stress management on pain.

In summary, behavioural interventions show promise to maintain or improve QOL following HCT. Importantly, no studies observed negative effects of interventions. The beneficial effects seen in HCT are supported by a larger literature examining behavioural interventions in oncology patients (Schmitz *et al*, 2005; Knobf *et al*, 2007). Additional research is now needed to demonstrate the effectiveness of these interventions on a larger scale. In the meantime, clinicians should consider recommending moderate-intensity aerobic exercise several times a week for patients who are able to engage in such activity and who may benefit from it. Clinicians should also consider a psychosocial referral for training in stress management for patients experiencing pain.

Discussion

Optimal care of HCT recipients requires a level of awareness and appreciation for QOL commensurate with the patients' own valuation of this important construct. As QOL plays a significant role in all phases of such patients' care, providers should make particular effort to both counsel prospective HCT patients on the potential threats to QOL as part of shared informed decision making, as well as regularly assess QOL in the ongoing follow up after this intensive treatment. In total, this requires an integration of knowledge of QOL, the practice of QOL assessment, as well as resources available for intervention into the usual clinical practice of providers caring for HCT recipients. To this end, we have reviewed QOL literature examining HCT in adults with haematological malignancies with the intention of providing a framework for patient education, clinical evaluation of QOL, as well as intervention to maintain or restore QOL after HCT.

For prospective HCT patients to make informed decisions about their treatment, they need to understand the nuances of

potential risks and benefits associated with their specific disease condition, the proposed transplantation procedures, as well as the risks incurred and beneficial outcomes possible with such treatment. We would proffer that a thorough understanding of the impact of HCT on QOL is just as important and relevant to this decision making process. In this discussion, it is important for providers to counsel patients on both the potential threats to QOL, as well as the positive outcomes and opportunity for growth that have been reported in the literature reviewed here to provide a balanced view of the impact of HCT. A focus on the specific abilities and limitations frequently encountered by HCT survivors is appropriate, and may help frame QOL issues in a way that patients can easily understand. It is also important for researchers to design and conduct QOL studies in such a way that results can be used for patient education. While longitudinal and comparative studies examining means and standard deviations on QOL scales are important, they can be difficult to translate into information that is easy for patients to understand. It is important for research to also focus on clinically significant change in QOL as well as the percentages of survivors who are ability to carry out specific, concrete tasks of daily living (e.g., carry groceries, walk up a flight of stairs, return to work or school). Data of this type provides a useful and intuitive way to disseminate study findings to patients and their families. While the importance of clinical utility in QOL research is starting to be recognized, (Frost *et al*, 2007; Guyatt *et al*, 2007) greater work is needed.

Clinical assessment of QOL provides an important opportunity to enhance patient-physician communication and promote proactive management of transplant-related side effects. We argue that clinical assessment of QOL should begin prior to HCT, wherein clinicians can first identify those patients who are at risk based on established risk factors for impaired QOL after HCT and continue through the survivorship period. An awareness of specific risk factors for poor QOL is important, including medical, demographic, and psychological risk factors. Future research should focus on the development of algorithms that identify HCT patients at risk for poor QOL. In addition, it is important to address potential threats to the QOL of partners of HCT recipients, as they appear to be an especially vulnerable, but integral part of the HCT recipient's recovery after HCT.(Bishop *et al*, 2007) Ongoing clinical assessment of QOL through office- or home-based computerized measures shows promise in the proactive management of QOL. These tools have the potential to improve physician-patient communication, patient satisfaction, symptom management, and QOL. These tools also show high acceptability to both patients and physicians. Interest in pursuing clinical assessment of QOL will probably continue to grow as dynamic methods of data capture evolve.

Finally, behavioural interventions including aerobic exercise programmes and psychosocial interventions have emerged as promising therapeutic modalities that are feasible, acceptable to patients, and result in improved outcomes with no adverse effects. The benefits of these modalities, as demonstrated in high-quality trials, include improvements in fatigue, pain, physical symptoms, as well as improvements in overall QOL. While the state of this research is maturing, reasonable recommendations based on the evidence to date would include moderate-intensity aerobic exercise several times a week alongside referral for physical therapy evaluation, and psychosocial referral for stress management in those patients experiencing pain. Prudent referral for these services and ongoing education, best achieved in a multi-disciplinary team dedicated to the care of HCT recipients, offers promise for improved QOL after HCT.

In summary, QOL is an important concern for patients throughout the transplant process, from early consideration of HCT as a treatment option to long-term survivorship. Although a sizeable literature exists describing QOL in patients treated with HCT, to date little effort has been made to integrate this knowledge into standard clinical practice. Greater attention is needed to reporting research findings in a way that can be easily communicated to patients. An additional focus should be on effectiveness and dissemination of current research regarding clinical assessment of QOL and behavioural interventions to improve QOL. The goal of these efforts is to seamlessly integrate QOL education, assessment and intervention into the spectrum of care currently provided to HCT patients.

Contribution

JP conducted literature search, analysis, and produced this manuscript. CA offered critical review of the manuscript. HJ contributed to the analysis, production of manuscript, and offered critical review.

Conflict of interest

The authors report no significant conflict of interest.

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