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ABSTRACT

Purpose
The aim of this study was to synthesise all qualitative evidence on the experiences of myeloma patients undergoing haematopoietic stem cell transplant (HSCT).

Method
A systematic search strategy was developed and a rigorous search of the literature was undertaken searching six databases (CINAHL, Embase, Medline, Psych Info, Ethos and Proquest). The software for systematic reviews www.covidence.org was used to blind screen for eligible papers. Quality appraisal of each study was undertaken using the Critical Appraisal Skills Programme (CASP). Confidence in each finding was assessed using Confidence in the Evidence from Reviews of Qualitative research (CERQual).

Results
Eight qualitative studies (reported in eleven papers and including seventy six myeloma patients) were selected in the final sample for evidence synthesis. Four themes were identified relating to patients’ feeling ‘dead’, disconnecting and isolating themselves, cognitive impairment and engagement with exercise and its benefits in recovery.

Conclusions
The burden of cognitive functioning among myeloma patients was often under detected. Nurses should ask patients regularly about their memory and any challenges they may be experiencing to their concentration and recall. Exercise during the transplant process can help improve patients’ recovery, both physically and psychologically. A structured exercise programme developed by a physiotherapist to suit the needs of each patient should be standard practice in the transplant process.

Key words: cognitive impairment, exercise, myeloma, transplant, qualitative, thematic synthesis.
Introduction

Multiple myeloma (also referred to as Myeloma) is a malignancy of plasma cells that originate from the B-cell lineage. It is characterised by the excess production of a monoclonal protein that subsequently results in different forms of end organ damage and the following symptoms; anaemia, renal insufficiency, hypercalcaemia and bone loss or destruction (Munshi and Anderson, 2013). Although consistent improvements in progression-free survival (PFS) and overall survival (OS) have been made in the last decade, myeloma remains an incurable condition (McEllistrim, et al., 2017). Administration of more intensive regimes such as haematopoietic stem cell transplant (HSCT) and the introduction of novel agents, has resulted in significant improvements seen in life expectancy and extended the median survival in all age groups by 50% with more significant improvement in the younger patient population (under 60 years) and predicted five and ten year survival estimates of more than 50% and 30% respectively (Boland et al., 2013).

Since the late 1990’s high dose melphalan treatment (200mg/m2) followed by autologous haematopoietic stem cell transplant (autoHSCT) (donor and recipient are the same person) has become the standard treatment for patients with myeloma aged less than sixty five years (Wang et al., 2014; Stettlar et al., 2017). While there has been some support for the use of allogenic HSCT in patients with multiple myeloma, this treatment option remains controversial with conflicting views on its role in the management of multiple myeloma (Koniarczyk et al., 2017).

The process of autoHSCT occurs over three phases: pre-transplant, transplant to engraftment and post-transplant (Koniarczyk et al., 2017). In the pre-transplant phase, mobilisation (e.g. using a granulocyte-colony stimulating factor) and collection of the patient’s haematopoietic stem cells occurs (HSCs). After high dose chemotherapy, the patient receives an infusion of their previously harvested HSCs. Toxicities experienced are due to high-dose melphalan.
which affects the gastrointestinal tract, bone marrow and hair follicles and requires intensive supportive care and psychological care (Koniarczyk et al., 2017).

Our understanding of the associated symptoms and treatment related toxicities with transplant among myeloma patients is limited (Ramsenthaler et al., 2016). There are many issues associated with autoHSCT that patients both fear and encounter. Although the risk of mortality with autologous transplant is low, it has a high emotional and physical morbidity with psychological and physical consequences that may last for months and even years and negatively impacts on their quality of life (QOL) and overall functioning (El-Jawahri et al., 2016). In a recent longitudinal study examining patient reported symptom burden during the 3-9 month period post autologous HSCT (Wang et al., 2015), it was found that 35% of patients consistently reported high burden symptoms of fatigue, pain, numbness, bone aches and muscle weakness up to nine months post autoHSCT.

Nurses play a pivotal role in educating, advocating and supporting patients and pre-empting potential co-morbid conditions associated with transplant in order to initiate early intervention to minimise side effects and associated distress (Bilotti et al., 2011). In order to care comprehensively for myeloma patients undergoing transplant, a deep insight into their experiences is also required. A recent qualitative systematic review focuses on myeloma patients’ experiences (Hauksdóttir et al., 2017), however, it does not focus specifically on myeloma patients’ experiences undergoing transplant. This study is therefore timely and is the only known qualitative evidence synthesis focusing specifically on myeloma patients undergoing transplantation.

**Methods**

The aim of this study was to describe the experiences of myeloma patients undergoing auto haematopoietic stem cell transplant (HSCT). Thematic synthesis of the qualitative literature as outlined by Thomas and Harden (2008) was the guiding methodology. This methodology
facilitates synthesis of findings across selected studies by the examination of the ‘results’ or ‘findings’ through coding by a line-by-line approach, following which descriptive themes and analytic themes are generated.

Search strategy
A systematic search was undertaken using all possible combinations of the study’s key words which included “myeloma patients”, “haematopoietic stem cell transplant”, “experience” and “qualitative” (Table 1). Six databases were searched (CINAHL, Embase, Medline, Psych Info, Ethos and Proquest). Year parameters were not set in order to capture all relevant literature. Grey matter such as unpublished material, e.g. PhD thesis and conference abstracts relevant to the question were also examined to avoid publication bias (EPPI-Centre, 2010). The initial search retrieved 1256 references.

Screening
Papers were included if they met the following inclusion criteria:

1. Patients with a diagnosis of myeloma who had undergone haematopoietic stem cell transplant.
2. Qualitative studies to include phenomenology, ethnography, grounded theory, generic qualitative or mixed methods which examine patients’ experiences.
3. Adult patients over 18 years of age
4. English language.

Following removal of duplicates, the title and abstract of all 1064 remaining papers were screened blindly by two reviewers (the first and last authors) in Covidence©, a software for systematic reviews (www.covidence.org). Conflicts were resolved by discussion and in some instances a third reviewer (an experienced oncology nurse) was consulted to confirm and agree with decisions. Twenty nine papers were selected for full text review. Following full-text review by the first and last authors, 18 articles were removed. (Figure 1).
**Included studies**

Eight studies (reported in eleven papers) were included for the final synthesis (Table 2). Seventy six myeloma patients were included in the eight studies reviewed. Most of the studies were undertaken in the US, with two from Australia and one each from the UK and Belgium. Two studies included homogeneous samples of all myeloma patients who had undergone HSCT (Coon and Coleman, 2014 a, b; Dahan and Auerbach, 2006). Two studies included all myeloma patients but not all had undergone HSCT (Craike et al., 2013, 2016; Portora et al., 2010, 2011). The remaining four studies had haematological heterogeneous samples including myeloma patients who had undergone HSCT. One included only one myeloma patient (Stephens, 2005), another two studies included two myeloma patients (Baker et al., 1999; Tarzian et al., 1999), and one study included five myeloma patients (Coolbradt and Grypdonck, 2010).

**Appraisal Process, data extraction and data analysis**

Free line-by-line coding of the findings of each of the eight studies was undertaken by the first and third author. The free codes generated independently by each author were discussed and following agreement were constructed into seven descriptive themes. Further cross-checking and merging of themes was then undertaken until the final stage of agreement on analytical theme generation (Thomas and Harden, 2008). Four principal analytical themes emerged from the analysis.

Quality appraisal was undertaken by the first and last authors in tandem with data extraction using the Critical Appraisal Skills Programme (CASP) (Table 3). Moreover, in order to determine overall confidence in the study findings, the Confidence in the Evidence from Reviews of Qualitative (CERQual) research approach was used (Lewin et al., 2015). The confidence in the study findings is assessed under the following headings: 1. Methodological
limitations; 2. Relevance; 3. Coherence, and 4. Adequacy (Table 4). Methodological
limitations refers to the extent of any concerns about the study design or conduct of the
included studies. Coherence is an assessment of how clear and well supported the fit is
between the data from the primary studies and the review. Adequacy is the overall
estimation of the richness and volume of data that supports the review’s findings. Relevance
refers to the extent to which the primary studies supporting the review are relevant in terms
of context (the population, phenomenon on interest and setting) as outlined in the evidence
synthesis question. The first and third author assessed each of the four CERQual
components and reached a decision of confidence on each review findings in terms of high,
moderate, low or very low (Lewin et al., 2015). An estimation of high and moderate
confidence for the findings was reached (Table 4).

Synthesis Findings

Four analytical themes were identified following analysis of the findings in the included studies:
‘dead man walking’, disconnecting and isolating, a ‘tired head’ and exercise for recovery.

‘Dead man walking’

Transplantation is a particularly demanding intervention both physically and psychologically.
The conditioning phase and post-transplant were distinct phases of the transplantation
process highlighted by patients. For some, the most distressing and difficult time was the time
between ablation of the bone marrow with intensive chemotherapy and the reinfusion of the
patient’s own stem cells to re-start bone marrow function; this time period was referred to by
patients as ‘looking’ or ‘being’ dead (Potrata et al., 2011). While patients reported feeling
fearful of dying they also reported that they felt they had actually ‘died’ (Potrata et al., 2011;
Coolbrandt and Grypdonck, 2010). In the post-transplant phase, the sense of an imminent
death remained and patients also described feeling ‘empty’ and fearful of a relapse (Dahan
and Auerbach, 2006; Coolbrandt and Grypdonck, 2010; Baker, 1999; Stephens, 2005). The
enduring threat of a relapse was ‘chronic worry’ and was like having ‘a weight placed over them’ (Dahan and Auerbach, 2006, p. 379).

**Disconnecting and isolating**

Difficult symptoms such as fatigue and nausea, although distressing, were seldom discussed and patients considered these an expected aspect of treatment and subsequent recovery (Potrata et al., 2011; Coon and Coleman, 2004; Coolbrandt and Grypdonck, 2010). Patients attempted to disconnect or isolate their thoughts to protect their psychological well-being (Coolbrandt and Grypdonck, 2010; Stephens, 2005; Tarzian, 1999). They tried to ban negative thoughts such as fear, sadness and anger which may have reduced the likelihood of a positive outcome (Coolbrandt and Grypdonck, 2010; Tarzian, 1999).

As aspect of disconnecting was a deliberate attempt to isolate themselves because they felt that it is up to them to get through the transplant irrespective of what family support they had (Baker et al, 1999; Dahan and Auerbach, 2006; Potrata et al., 2011). When patients underwent HSCT they had a sense of physical deterioration and vulnerability and expressed anger, although some patients chose to internalise the anger while others directed it at family members (Dahan and Auerbach, 2006; Baker et al., 1999). Some also chose to withhold information from their family regarding how unwell they really felt (Stephens, 2005; Dahan and Auerbach, 2006).

**A ‘tired head’**

Cognitive changes were common among patients (Potrata et al., 2010, Baker et al, 1999). Poor recall, problems with short-term memory and poor concentration were experienced. These were often permanent and interfered with daily life (Portora et al., 2010). Some patients did not even remember having met the researcher previously even when reminded (Portora et al. 2010). Struggling to find words and make sentences was a common occurrence and this was also among patients who had university education (Portora et al., 2010). Coping strategies employed by patients included keeping detailed notes, reading children’s books and
shorter texts and using talking books (Portora et al., 2010). Patients who had undergone multiple previous treatments were more affected (Baker et al., 1999; Portrata et al., 2010). Fatigue, a common and debilitating physical symptom (Portrata et al., 2010; Dahan and Auerbach, 2006; Baker et al., 1999) also contributed to cognitive impairment and associated depression (Portrata et al., 2010.). Exercise was found to have cognitive benefits (Craike et al., 2013)

**Exercise for recovery**

Some patients believed that challenging their limits enhanced their progress and contributed to their recovery (Coolbrandt and Grypdonck, 2010). Emphasis on exercise to enhance recovery was evident (Coon and Coleman 2004a,b; Craike et al 2013, 2016;). Patients generally wanted more information on exercise and preferred health care professionals with knowledge of myeloma to provide this information, such as GPs, haematologists, nurses, physiotherapists and occupational therapists (Craike et al., 2016). Physiotherapists were believed to be the most suitable to design and run an exercise programme (Craike et al, 2016).

Walking was the exercise most popular and preferred among myeloma patients (Coon and Coleman, 2004a; Craike et al., 2013, 2016). Other preferred types of exercise included yoga, Pilates, aerobics, strength training, gardening, tai chi, tennis and table tennis (Craike et al., 2013, 2016). Many patients also expressed a preference for the location of an exercise programme to be their treating hospital, however, an equal number also preferred a home-base programme (Craike et al., 2016). Patients also wanted the exercise programme to be individualised for them following a physical assessment (Craike et al., 2016).

A motivating factor for patients to enrol in an exercise trial was the knowledge that exercise for important “to getting well” (Coon and Coleman, 2004a, p. 114) and would be good for them to help them get through the transplantation journey (Coon and Coleman, 2004b). However, some patients who had a transplant believed that undergoing an exercise programme during
the treatment would not be feasible (Craike et al., 2016). This was the view of all patients in Coon and Coleman's study irrespective of patients' exercise history.

Another motivation factor to participate in an exercise programme was the administration of prophylactic epoetin alfa (Procrit) (Coon and Coleman, 2014a) and patients' belief that this would positively influence their ability to exercise (Coon and Coleman, 2014b). However, nausea was the symptom most likely to interfere with exercise adherence (Coon and Coleman, 2014a). Another major barrier to exercise was fatigue (Coon and Coleman, 2014a; Craike et al., 2013). Fatigue was most commonly experienced by patients who had undergone HCST when compared to myeloma patients who had been treated with chemotherapy and/or radiotherapy (Craike et al., 2013). Other lesser barriers to exercise included shortness of breath, pain, abnormal tolerance to heat, fever/fear of infection, thromboembolism (Coon and Coleman, 2014a; Craike et al., 2013), bone pain and fear of bone fractures and poor concentration (Craike et al., 2013). While many myeloma patients have significant bone involvement due to their disease, this was not seen by patients as a barrier to exercise (Coon and Coleman, 2014a). In addition, those with back pain found walking helpful in relieving pain (Coon and Coleman, 2004a).

Many described how exercise helped them to gain strength in the post-transplant phase and described the increase in physical activity with an associated physical vitality (Craike et al., 2013). Exercise also helped combat fatigue and facilitated patients returning to a normal life (Craike et al., 2013). The focus of physical recovery was on avoiding deterioration in health and function and some patients engaged in physical activity which allowed them to regain some routine and feel a bit more ‘normal’ (Craike et al., 2013; Coon and Coleman, 2004). Support from family was also a motivating factor for engagement in an exercise programme (Coon and Coleman, 2014a). Patients also used exercise as a way to connect with friends and family (Craike et al., 2013). However, patients admitted that they found it hard to find the time to exercise due to all the appointments required to check their bloods (Coon and Coleman, 2014a).
DISCUSSION
This qualitative thematic synthesis provides the first known systematic overview of qualitative studies exploring the experiences of myeloma patients who have undergone autoHSCT. A major strength of this methodology is the aggregation of conclusions drawn from a range of studies which can be used to guide policy makers. Quality assessment of the studies reviewed (Table 3) ascertained that most were of high quality. Confidence in the Evidence from Reviews of Qualitative (CERQual) revealed high confidence in one theme ‘exercise for recovery’ and medium confidence for all other themes (Table 4).

The findings presented could be discussed in information sessions with patients before they undergo their transplant. The information patients receive is strongly emphasised on the transplant process itself but less so for life after transplant and the challenges posed (Tarzian et al., 1999); and these findings presented here will help in addressing this gap.

The most distressing and challenging time for patients was the time between intensive chemotherapy when their bone marrow was eradicated and they received their stem cells (conditioning phase). During this period, patients referred to their fear of death and at times actually felt like they had died although they did not discuss clinical death, it is the period that is reported as most difficult and most isolating (Potrata et al., 2011). This feeling of death associated with stem cell transplant warrants further evaluation as it would be important to determine the difference between reasonable fear of intensive chemotherapy and the fear of death and other complex feelings of loss of autonomy and/or loss of control. Further research on this could adopt an ethnographic approach which would allow a ‘window’ into the sociocultural context of stem cell transplant.

Importantly, this review has shown that the prevalence and burden of cognitive functioning among myeloma patients post-transplant was under appreciated and often under detected. Myeloma patients endure not one but many treatments which may have a cumulative effect on memory (Potrata et al., 2011). Cognitive impairments also appear to be strongly linked to fatigue, anaemia and depression, which are common consequences of myeloma treatment. It
is likely that patients do not discuss cognitive impairment as they are not asked about it by staff as a side effect of treatment (Portora et al., 2010). Nurses should ask patients regularly about their memory and any challenges they may be experiencing to their concentration and recall,

It is well known that neurocognitive deficits (referred to as “chemo brain”), have a huge impact on allogenic transplantation survivors’ daily activities and a challenge for those who return to work (Inamoto, & Lee 2017; Clavert et al., 2017). Our understanding of neurocognitive effects following autologous transplantation is also of concern. Jones et al (2013) reported that 47.2% (25/53) of myeloma patients displayed cognitive impairment after induction (pre-AuHSCT) and this impairment maintained at a high level over time with 49% of patients at 1 month and 48% at 3 months post-autoHSCT displaying cognitive impairment.

It has been established that there is a common link between fatigue, depression and cognitive impairment among myeloma patients (Ramsenthaler et al., 2016). However, patients may not readily recognise their cognitive impairment and it is argued that patients’ cognitive complaints may manifest in feelings of anxiety, depression and fatigue as opposed to cognitive decline (Klein et al., 2008). Most adult survivors recover their cognitive function within one year after transplant, but milder impairments can be evident up to five years post-transplant for some survivors (Bevans et al., 2017). Despite the prevalence of cognitive impairment and how distressing it is for patients, this symptom has not been widely acknowledged by oncology healthcare professionals (Potrata et al., 2010).

Recent data highlights the importance of physical activity, diet and weight control in long term HSCT survivors and acknowledges the associated increased cardiovascular risk in this patient cohort (Chow et al., 2014). Physical exercise was highlighted as being of great benefit to myeloma patients to help overcome the impact of treatment and symptoms (Coon and Coleman, 2004a,b; Craike et al., 2013, 2016). In consultation with a physiotherapist, patients’ pre-treatment level of physical activity should be assessed and an individualised programme
developed. Moreover, haematology units should examine the possibility of providing exercise equipment in their units (Craike et al., 2013). Evidence-based guidelines on exercise for myeloma patients focus on ensuring that exercise is part of care pathway before and after rehabilitation (Snowden et al., 2017). Further research is needed to examine the role of physical activity in overall wellbeing for myeloma patients during the transplant process and determine its positive effects on levels of fatigue, pain, anxiety, cognitive impairment and depression.

Ongoing education regarding life after transplant and extended recovery should be integrated into nurses’ education programmes for patients. This should include providing sufficient time to encourage patients express their views on what they think recovery will entail and what skills they think they have to help them in their recovery. An individual plan can then be developed tailored to each patient’s perceived needs.

Study Limitations

The search strategy was purposively sensitive, therefore aimed at including all relevant literature. However, it was limited to peer-reviewed articles and reports published in the English language only. The heterogeneity of the study samples in four studies is also a limitation of this review (Baker et al., 1999; Coolbrandt and Grypdonck, 2010; Stephens, 2005; Tarzian et al., 1999). Moreover, these studies did not highlight which narratives were from myeloma patients. However, the inclusion of these studies fitted with our use of criterion sampling, an approach often used in qualitative evidence synthesis to ‘construct a comprehensive understanding of all the studies that meet certain pre-determined criteria’ (Suri, 2011, p.69). We aimed for inclusivity and therefore did not apply criteria for selecting only studies with the best evidence as outlined by Aslam et al. (2017) who illustrate their use of the CART criteria (comprehensiveness, accuracy, relevance, timeliness) (Tennison, 2006), employed when there is a large number of studies.
CONCLUSIONS
This is the first known qualitative synthesis of myeloma patients’ experiences of autoHSCT.
The findings presented can be used by specialist nurses when providing information for
myeloma patients for their transplant. Although autoHSCT remains common practice in the
treatment of myeloma patients, insight into patients’ experiences remain under appreciated,
especially in extended recovery post-transplant. Further research is needed on patients’
longer-term experiences of cognitive impairment and the effects of exercise on overall
wellbeing and recovery.
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