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Chronic Fatigue in Myelodysplastic Syndromes: Looking Beyond Anemia

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Biographies

Dr. Callum Brownstein, PhD, is a post-doctoral researcher at University Jean Monnet, Saint Etienne, France. He completed his PhD at Northumbria University, Newcastle, U.K, where he assessed recovery of neuromuscular function following high-intensity intermittent exercise. His current research focuses on the acute neuromuscular responses to exercise, and the etiology of chronic fatigue implicated in various pathologies.

Dr. Elisabeth Daguenet obtained her PhD in Molecular and Cellular Aspect of Biology at the Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), France. Subsequently, in 2013 Elisabeth moved to Barcelona (Spain) to the Centro de Regulacio Genomica (CRG) to work on the regulation of alternative splicing by long non-coding RNAs. In February 2017, Elisabeth relocated to the Institut de Cancérologie Lucien Neuwirth as a Clinical Project Manager in Hematology.

Denis Guyotat, MD, PhD, is a Professor of Haematology at University Jean Monnet, and the Head of the Department of Haematology and Cell therapy at the Lucien Neuwirth Cancer Institute, in Saint-Etienne, France. After graduating in the University of Lyon, he completed his training in stem cell transplantation in London (UK) and Seattle (USA) before moving to Saint-Etienne. His main scientific interests are the treatment of acute leukaemias and stem cell transplantation, and the pathophysiology of acute myeloid leukaemia and myelodysplastic syndromes.

Dr. Guillaume Millet, PhD, is a Professor of Exercise Physiology at Jean Monnet University in Saint-Etienne (France). After graduating from the University of Franche-Comte in 1997, he has held various positions in Dijon, Saint-Etienne and Grenoble. Between 2013 and 2018, he was a Professor in the Human Performance Laboratory and the Faculty of Kinesiology, University of Calgary (Canada) where he led a research group on neuromuscular fatigue. In 2019, he was named at the Institut Universitaire de France as a Senior member. His general research area investigates the physiological, neurophysiological and biomechanical factors associated with fatigue, both in extreme exercise (ultra-endurance, hypoxia) and patients (neuromuscular diseases, cancer, multiple sclerosis).

SUMMARY

Chronic fatigue is the most common and severe symptoms in myelodysplastic syndromes (MDS) and has a strong negative association with health-related quality of life (HRQoL). Despite anemia being the most common objective manifestation of MDS, and the associated link between anemia and fatigue, evidence on treatments which temporarily mitigate anemia is equivocal regarding the effects on fatigue. Previous work has found weak associations between anemia and chronic fatigue in MDS. As such, given that improving HRQoL is one of the primary treatment aims in MDS, further work is required to identify other potential contributors to chronic fatigue in these patients. In addition to anemia, MDS is associated with numerous other deviations in physiological homeostasis and has negative psychological consequences with links to chronic fatigue. Accordingly, the present review provides several potential aetiologic agents relevant to chronic fatigue in MDS which can be used to guide further research in this field.

INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogeneous group of hematopoietic stem cell neoplasms characterised by ineffective hematopoiesis, leading to blood cytopenias and an increased risk of progression to acute myeloid leukaemia (AML) (Gangat et al., 2016). Although MDS can affect people of any age, it is most prevalent in older individuals, with a median age at diagnosis of 65-70 years (Ades et al., 2014; Tinsley et al., 2017). The incidence of MDS has been estimated as approximately 3-4 per 100,000 population per year, and around 30 cases per 100,000 per year among patients over 70 years of age, though it is believed that this figure could be higher due to underreporting and underdiagnoses of MDS (Cogle, 2015). The prevalence of MDS is estimated at 60,000 to 170,000 in the United States, and is projected to grow, likely due to an improving awareness on the requirement to report MDS cases (Cogle, 2015). While the precise causes of MDS are incompletely understood, approximately 15-20% of MDS cases are related to genetic damage incurred through previous exposure to radiation and/or chemotherapy, and it is hypothesized that age-related accumulation of genetic damage results in mutations in cellular pathways implicated in MDS (Gangat et al., 2016).

The clinical presentation of MDS is highly variable, ranging from patients who are asymptomatic and have a life expectancy similar to the general population, to symptomatic patients with a high risk of progression to AML (Efficace et al., 2015b), an aggressive type of cancer associated with high mortality rates (Hofmann and Koefler, 2005). Indeed, it has been reported that 50% of MDS patients are asymptomatic at diagnosis (Hofmann and Koefler, 2005). Due to the high variability in the course of the disease, patients with MDS are categorized into four distinct risk groups based on outcome measures included in the International Prognostic Scoring System (IPSS), which consists of clinical and laboratory variables including: percentage of bone marrow blasts, number of peripheral cytopenias (i.e.,

hemoglobin, neutrophil cell counts and platelet counts) and cytogenetic abnormalities (Ades et al., 2014). Each of these variables has a relative risk score, which combine to stratify patients into one of the four risk groups based on risk of transformation to AML and in relation to overall survival. The risk groups include: low-risk, intermediate-1-risk, intermediate-2-risk, and high-risk (Efficace et al., 2015b; Greenberg et al., 1997). Median survival rates for low-, intermediate-1-, intermediate-2- and high-risk MDS are 5.7, 3.5, 1.2 and 0.4 years, respectively (Greenberg et al., 1997). The majority of MDS patients belong to the lower risk categories, with around 80% of MDS cases estimated as either low- or intermediate-1-risk (Santini, 2016). The IPSS has since been revised (IPSS-R) (Greenberg et al., 2012) to include more parameters, such as blast percentages, comprehensive cytogenetic classifications, and depth of cytopenias. The IPSS-R, which groups patients into five risk groups (very low-, low-, intermediate-, high-, very high-risk), was shown to have improved prediction power for prognosis assessment in MDS patients relative to the original IPSS (Greenberg et al., 2012). While risk stratification can facilitate decision making regarding treatment and management of MDS, clinical decision making remains a challenging prospect in this population (Efficace et al., 2014; Stauder, 2012). This is due in large part to the old age at which patients are most commonly diagnosed, and high diversity of elderly patients with respect to health status, pre-existing comorbidities, and perceived ability to tolerate specific treatments, particularly those which are more aggressive (Efficace et al., 2014; Stauder, 2012).

Fatigue in Myelodysplastic Syndromes

Symptoms of MDS are dependent on the severity of the condition, but include bruising or excessive bleeding, increased risk of infection, pain, dyspnea, insomnia, angina pectoris and

chronic fatigue (Schuler et al., 2016). The latter of these symptoms, characterised by feelings of tiredness, weakness, lethargy and decreased mental alertness, is consistently reported as the most frequent and debilitating symptom in MDS patients. For example, in a group of 280 newly diagnosed higher-risk MDS patients (intermediate-2 and high-risk), Efficace *et al.* (2015a) found that 92% suffered from chronic fatigue as measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), with 28% of patients reporting moderate to severe fatigue. In 145 MDS patients of all risk-groups, Escalante *et al.* (2019) reported that the average score using the Functional Assessment of Cancer Therapy-Fatigue (FACIT-F) was 25. Using this scale, a higher score (out of 52, based on 13 fatigue-related questions with Likert scales from 0-4) reflects less fatigue, with any score < 34 recommended as the cut off value for diagnosis of chronic fatigue based on results from validation studies (Van Belle et al., 2005). Accordingly, the average score of 25 obtained by Escalante *et al.* (2019) highlights the severe nature of chronic fatigue in many MDS patients. Moreover, in a recent study, Efficace *et al.* (2020) used the FACIT-F to compare fatigue in MDS patients (n = 927) across the 5 risk-groups included in the IPSS-R, with the FACIT-F score of each group also compared with that of an aged-matched general population (n = 1075). The FACIT-F score was progressively lower (indicating greater fatigue) for each of the 5 risk groups, indicating that severity of MDS is associated with the severity of chronic fatigue. Moreover, in IPSS-R risk groups from low- to very-high risk, fatigue was significantly higher in MDS patients compared with the aged-matched population, with the difference in score considered clinically meaningful.

As with many chronic conditions, the fatigue experienced by the majority of MDS patients can have widespread consequences on many aspects of daily living. The plight of fatigue in this patient group was emphasized through qualitative research by Thomas (2012), who interviewed patients concerning the effect of MDS on physical, functional, social and

emotional well-being. Patients were quoted as stating that MDS resulted in “a deterioration of what you were able to do before”, difficulties in tasks of daily living such as climbing stairs, impaired ability to socialize, and consequently, frustration and depression at their activity restriction (Thomas, 2012). Indeed, health related quality of life (HRQoL) is substantially lower in MDS patients compared with age- and sex-matched controls (Stauder et al., 2018), with fatigue representing the primary factor impairing HRQoL (Efficace et al., 2015a). Furthermore, recent work reported that self-reported chronic fatigue in intermediate and higher-risk MDS patient was an independent predictor of survival beyond gold-standard prognostic indices in newly diagnosed MDS patients (Efficace et al., 2015b). Given that one of the primary aims of treatment in MDS patients is to improve HRQoL (Fenaux et al., 2019), the primary barrier to which is fatigue, understanding the aetiology of chronic fatigue in MDS patients is imperative in order to devise strategies to attenuate these mechanisms and alleviate fatigue symptoms in this patient group. Accordingly, the aim of the present review is to highlight the main potential contributors to chronic fatigue in MDS patients. Specifically, we suggest that, given that a number of studies have reported either a modest link (Jansen et al., 2003), or no link (Steensma et al., 2008) between anemia and chronic fatigue, and that treatments which temporarily resolve anemia do not always ameliorate fatigue (Casadevall et al., 2004; Spiriti et al., 2005), a greater focus on mechanisms beyond anemia is warranted.

Aetiology of Fatigue in Myelodysplastic Syndromes

The aetiology of fatigue reported in MDS patients is incompletely understood. The section below highlights some of the potential etiological agents of fatigue in MDS patients. It should be noted that many of the potential explanatory mechanisms behind MDS-related fatigue are interrelated, such as anemia, inflammation, oxidative stress, impaired cardiovascular

function, and increased fatigability, which refers to fatigue in the context of activity (Kim et al., 2018). Consequently, research investigating factors associated with fatigue in MDS using a comprehensive group of objective and subjective assessments is warranted in order to provide an understanding on how to better manage fatigue in this population. Figure 1 summarizes the potential contributors to chronic fatigue in MDS patients based on the numerous physiological abnormalities associated with this condition.

Anemia

The primary candidate to explain fatigue in MDS patients is anemia. Preliminary data from the European MDS Registry in low- and intermediate-1-risk patients report that 87% had anemia according to World Health Organisation (WHO) criteria (< 120 g/L), with 63% displaying Hb values below 100 g/L (Castelli et al., 2018; de Swart et al., 2015). Anemia in MDS patients is generally treated initially with erythropoietin-stimulating agents (ESAs), and later through blood transfusions, with more than 80% of patients requiring red blood cell (RBC) transfusions throughout the course of the disease, and 40% of anemic patients becoming transfusion dependent (defined as the requirement of blood transfusion every 8 weeks or less) (Efficace et al., 2015a). Conflicting evidence exists on the relationship between fatigue and anemia in MDS patients, with this evidence summarized in Table 1. For example, in transfusion dependent MDS patients, Jansen *et al.* (2003) found a significant correlation between Hb levels and physical (Spearman's correlation coefficient = -0.31) and mental fatigue (Spearman's correlation coefficient = -0.26), while Efficace *et al.* (2015a) found that Hb was an independent predictor of chronic fatigue in higher risk patients, but could not fully explain this symptom (Beta regression coefficient = 0.14 using FACI-F scale). In contrast, Steensma et al. (2008) found no significant correlation between Hb and self-

perceived fatigue (Spearman's correlation coefficient = -0.05). Moreover, studies investigating the effects of interventions which transiently alleviate anemia, such as erythropoiesis stimulating agents (ESAs) and RBC transfusions have produced equivocal results. For example, even when Hb levels are increased through ESAs or blood transfusions, fatigue often persists in many patients. Casadevall *et al.* (2004) investigated anemia and HRQoL in 24 lower-risk MDS patients in response to recombinant human erythropoietin (rHuEPO) alone and in conjunction with human granulocyte-colony-stimulating factor (rHuG-CSF). Despite 42% of participants exhibiting erythroid responses, no effect on HRQoL or fatigue was demonstrated. In a randomized prospective controlled trial, Greenberg *et al.* (2009) assessed erythroid responses and HRQoL in lower risk MDS patients in response to EPO with or without rHuG-CSF ($n = 53$) compared with supportive care alone ($n = 57$). Although no significant differences in fatigue scores were noted between participants assigned to EPO and those assigned to supportive care, patients who had an erythroid response reported significant improvements in fatigue, as well as physical, emotional and functional well-being and overall HRQoL. In a study evaluating the impact of epoetin alfa on Hb levels and QOL in 133 patients with low-risk MDS, Spiriti *et al.* (2005) showed a 68% erythroid response rate following 8 weeks of treatment, with a concurrent improvement in HRQoL and fatigue, and a positive correlation between Hb changes and corresponding changes in HRQoL following 8 weeks of treatment, though the association was not strong (Pearson's correlation coefficient = 0.28 at week 8; $P = 0.01$). Accordingly, it is evident that ameliorating anemia will likely improve fatigue and HRQoL in MDS patients, but will not eliminate symptoms of fatigue in all patients.

Despite the equivocal results surrounding anemia and chronic fatigue in MDS, fatigue is seen as a hallmark symptom of anemia, and indeed there is a mechanistically plausible link between anemia and fatigue. For example, the anemia experienced in MDS patients impedes

oxygen carrying capacity and provokes a higher cardiac and respiratory demand to sustain adequate oxygen supply during rest and physical activity. Furthermore, limited oxygen supply in MDS patients could lead to tissue deoxygenation and an augmented metabolic stress during low-intensity physical activity that is commonplace in activities of daily living. In addition, it has been shown that lower Hb levels can be associated with structural and functional changes in capillarity and muscular fibers (Deveci et al., 2001; Hepple, 2000). For example, a study on 909 participants aged 65 and older found a significant association between Hb and skeletal muscle density, area and strength (Cesari et al., 2004). Anemia-related impairments in muscle strength would again impair the ability to perform everyday activities. Furthermore, anemia is also associated with increased formation of reactive oxygen species under hypoxic conditions (Grune et al., 2000), which could further impair contractile function (see 'Oxidative Stress' section). Accordingly, the well-established link between anemia and chronic fatigue is likely explained, at least in part, by increased fatigability, leading to an augmented deterioration in physical capacity during tasks of daily living and consequently causing fatigue to accumulate during such activities (Bailey et al., 2012; Twomey et al., 2017). Nevertheless, the conflicting results surrounding the effects of attenuating anemia on fatigue in MDS, along with the either absent (Steensma et al., 2008) or weak link between Hb and fatigue (Jansen et al., 2003) described above, highlight the requirement for a greater understanding of the aetiology of MDS-related fatigue and an identification of factors other than anemia that might contribute to this symptom.

Table 1. Results from studies exploring the relationship between haemoglobin concentrations and chronic fatigue in myelodysplastic syndrome (MDS) patients.

Author	N	Age (median)	Risk classification	Time since diagnosis (mean)	Fatigue scale	Statistic	Correlation coefficient	P-value
Jansen <i>et al.</i> (2003)	50	73	Not reported (transfusion dependent)	Not reported	MFI	Spearman's rank correlation coefficient	General fatigue ($R_s = -0.11$) Physical fatigue ($R_s = -0.31$) Mental fatigue ($R_s = -0.26$)	General fatigue ($P = 0.46$) Physical fatigue ($P = 0.03$) Mental fatigue ($P = 0.07$)
Efficace <i>et al.</i> (2015a)	280	71	Higher-risk	≤ 6 months	FACIT-F	Beta coefficient	FACIT-F score ($\beta = 0.14$)	$P < 0.001$
Steensma <i>et al.</i> (2008)	359	66	Not reported	12 months	BFI and FACT-An fatigue subscale	Spearman's rank correlation coefficient	BFI score ($R_s = -0.05$) FACT-An fatigue score ($R_s = 0.04$)	BFI score ($P = 0.48$) FACT-An fatigue score ($P = 0.54$)

MFI = multidimensional fatigue inventory, FACIT-F = functional assessment of chronic illness therapy fatigue scale, FACT-An functional assessment of chronic illness therapy anaemia questionnaire, BFI = brief fatigue inventory, R_s = spearman's rank correlation coefficient, β = beta coefficient.

Inflammation

Inflammatory dysregulation is considered one of the driving forces in the pathogenesis of MDS (Ganan-Gomez et al., 2015). For example, mounting evidence indicates that inflammatory and autoimmune disorders increase the risk of development of MDS, possibly through direct damage to bone marrow precursors and induction of malignant transformation (Ganan-Gomez et al., 2015). The presence of abnormal levels of markers of inflammation in the peripheral blood of MDS patients is well-documented. Indeed, a recent meta-analysis including data from 697 patients across 11 studies found that levels of tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6) and IL-8 were higher in MDS patients compared with controls (Shi et al., 2019), indicating a profound dysregulation of inflammatory signaling. It is well-established that cytokines are heavily involved in ‘sickness behavior’, the coordinated set of adaptive behavioral changes that occur in infected individuals to promote survival, a major component of which is an increase in fatigue (Larson and Dunn, 2001). Causal links between inflammation and fatigue have been demonstrated using animal models in which the symptoms of fatigue and reduced motivation appear after induction of high levels of pro-inflammatory cytokines, such as IL-1 (Dantzer et al., 2014). In humans, treatments which reduce inflammation, such as antagonists of TNF- α , have also been shown to reduce fatigue in patients with rheumatoid arthritis or psoriasis (LaVoy et al., 2016; Tyring et al., 2006). While mechanisms by which inflammation can interfere with brain function to induce fatigue are incompletely understood, it is known that inflammatory cytokines have an ability to cross the blood-brain barrier and modulate brain function. For example, IL-1 has many receptors in diverse areas of the brain, with an abundance of receptors located on the hypothalamus (Larson and Dunn, 2001; Meyers et al., 2005). In turn, the hypothalamus has rich connections with the brain stem, frontal cortex, and limbic system, areas involved in emotion, behavior, motivation, memory and motor dexterity. Other inflammatory markers, such as IL-6 and

TNF- α , also exhibit neuromodulatory properties which have been discussed as major factors in fatigue (Carmichael et al., 2006; Proschinger and Freese, 2019). Thus, one proposed mechanism is that cytokines can cross the blood-brain barrier and bind to receptors to exert modulatory effects on areas of the brain involved in emotions, mood, cognition, motivation, which in turn could contribute to fatigue. Alternatively, it has been suggested that cytokines could act on brain endothelial cells activating cyclooxygenase, enabling the synthesis of prostaglandins, which could readily cross the endothelial barrier to penetrate the brain parenchyma (Dantzer et al., 2014). Vagally-mediated pathways, in which peripheral cytokines such as IL-1 activate vagal afferents to bypass the blood-brain barrier, have also been proposed (Larson and Dunn, 2001). Whatever the mechanism, there is good evidence to support the direct influence of inflammation of fatigue. In addition, correlations between fatigue and several inflammatory markers have been reported in a number of other cancer types (Saligan et al., 2015; Schubert et al., 2007). In MDS patients specifically, the serum concentrations of IL-1, IL-6 and TNF- α are correlated with fatigue (Meyers et al., 2005). Consequently, it is evident that inflammation could be a contributor to fatigue in MDS patients, and further research into the link between inflammation and fatigue in this patient group is warranted.

Oxidative stress

Oxidative stress is a state in which reactive oxygen species (ROS) are produced at a rate that exceeds cellular protective, adaptive and repair capacities, resulting in damage to local tissues, including lipid membranes, protein structures, and nucleic acids. The presence of oxidative stress in many MDS patients has been established (Farquhar and Bowen, 2003), with heightened oxidative stress markers reported in 85% of MDS patients compared with

reference ranges of ROS (Saigo et al., 2011). The increased oxidative stress is thought to be related to over-accumulation of iron molecules mediated by RBC transfusion and a decrease in hepcidin, a key iron-regulatory hormone, and/or increased activity of TNF- α , which is known as a producer of free radicals (Peddie et al., 1997). There are a number of mechanisms by which oxidative stress could contribute to fatigue in MDS. One potential mechanism could be through oxidative stress-induced endothelial dysfunction and diminished vasodilator capacity. A molecule integral to healthy endothelial function is nitric oxide (NO), which is produced within endothelium by nitric oxide synthase. Vascular NO induces dilation of blood vessels, prevents platelet aggregation and adhesion, and limits oxidation of low-density lipoprotein (LDL) (Forstermann, 2010). The ROS play a major role in NO-based cell signaling, and ROS can affect NO availability both from production to post-production scavenging. Indeed, a link between oxidative stress and hypertension has been demonstrated, thought to be due in part to inactivation of NO (Ghosh et al., 2004). In turn, the oxidative stress-mediated impairment in vascular function could impede oxygen delivery and utilization at the peripheral level, and thereby compound cardiovascular and metabolic stress during physical activity and contribute to an increased fatigability.

In addition to perturbations in vascular function as a result of oxidative stress, heightened concentrations of ROS and reactive nitrogen species (RNS) have been demonstrated to interfere with contractile function both through direct interference with myofibrillar function (Moopanar and Allen, 2005; Reid, 2008), as well as directly impairing calcium release (Cheng et al., 2016). Indeed, heightened concentrations of ROS/RNS have been demonstrated to elicit prolonged low-frequency force depression (Cheng et al., 2016), which is the force response when a muscle is stimulated electrically at low-stimulation frequencies (i.e. ~10-20 Hz, with stimuli being separated by ~100 ms). Given that this frequency of stimuli is similar to the frequency at which the motor neurons activate muscle fibres during voluntary

contractions (Jones, 1996), the implication of a reduced force response to low-frequency stimulation is that a higher level of neural drive to the muscle would be required to achieve the same submaximal force output (Dundon et al., 2008; Keeton and Binder-Macleod, 2006). In turn, the higher efferent command associated with the increased neural drive gives rise to corollary discharge, which activates sensory areas within the brain and in turn influences perceptions of effort during physical activity (Twomey et al., 2017). Consequently, given the higher ROS generation in MDS patients, it is possible that oxidative stress could contribute to chronic fatigue in MDS through interference with contractile function. Taking these factors into consideration, the potential effects of oxidative stress on both vascular and contractile function could lead to impairments in physical capacities and increased fatigability. In turn, this could cause perceptual fatigue to accumulate when performing repetitive tasks of daily living due to exacerbated impairments in physical function during activity (Twomey et al., 2017).

Sleep disorders

Sleep disturbance is widely recognized to contribute to fatigue and impaired HRQoL in patients with various forms of cancer (Palesh et al., 2010; Roscoe et al., 2007). Similarly, sleep disturbance has been reported in patients with MDS and is associated with both fatigue and overall survival (Luskin et al., 2017). Specifically, in 251 newly diagnosed MDS patients, Luskin *et al.* (2017) found that 53% of patients reported some level of sleep disturbance, with an independent association found between sleep disturbance and fatigue even when controlling for comorbidity, anemia, and other measures of disease risk. Furthermore, the study reported independent associations between sleep disturbance and overall survival, as well as fatigue and overall survival. Moreover, Efficace *et al.* (2015a)

found that 50% of fatigued MDS patients reported high levels of insomnia. However, these studies used self-report questionnaires alone to evaluate sleep quality, with no studies measuring sleep disturbances using objective measures in MDS patients. Given that differences have been reported between self-reported sleep and objective measures of sleep such as those measured using actigraphy (Girschik et al., 2012), and the link between sleep disturbance and overall survival in MDS (Luskin et al., 2017), further research is warranted to more accurately determine the relationship between sleep disturbance and fatigue in MDS patients.

Physical deconditioning

Another contributory candidate to chronic fatigue in MDS patients is impairments in physical conditioning. As discussed previously, the anemia associated with MDS has implications for the ability to transport and utilize oxygen, as well as increased oxidative stress (Grune et al., 2000), thus increasing the cardiovascular and metabolic demand of low-intensity physical activity that is commonplace in activities of daily living. Neuromuscular complications could also arise due to anemia (Deveci et al., 2001), oxidative stress (Cheng et al., 2016) and inflammation (Carmichael et al., 2006; Reid, 2008; Reid and Moylan, 2011), potentially compromising muscle size, contractility and strength. Taken together, the physical deconditioning concurrent with symptoms of MDS could contribute to fatigue through both an increase in physiological stress and in the perception of effort required to complete everyday tasks, such as walking, lifting, carrying or climbing stairs, as indeed was highlighted through patient interviews (Thomas, 2012). In turn, this could lead to avoidance of physical activity which could further exacerbate physical deconditioning and thereby fatigue (Kuppuswamy, 2017; Twomey et al., 2017), and/or a compounded deterioration in

physical function during successive activities of daily living, thereby increasing perceptions of fatigue throughout the day (Twomey et al., 2017).

At present, no data exist concerning the habitual physical activity levels of MDS patients. Moreover, no studies have assessed the possible association between physical function and chronic fatigue in MDS patients, though poor physical performance using a 'sit-up and go' test (Podsiadlo and Richardson, 1991) was shown to be associated with poor survival outcomes in MDS and AML patients (Deschler et al., 2013). Given the proposed link between physical function, fatigability and chronic fatigue (Twomey et al., 2017), research exploring the relationship between physical capacity using traditional measures of cardiorespiratory function [e.g. maximal oxygen consumption (VO_{2max}) and ventilatory thresholds (VTs)], neuromuscular function and exercise capacity in MDS patients is warranted.

Psychosocial factors

In addition to physiological perturbations associated with MDS, psychosocial factors could also be implicated in fatigue in this population. The disease-burden associated with MDS, including the time and effort required to cope with the disease, such as frequent visits to doctors and managing side effects, substantially impair quality of life (Heptinstall, 2008). Indeed, qualitative data from MDS patients indicate that those living with the disease perceive a "loss of life control" due to the symptoms and management of the disease (Thomas, 2012). Such factors are likely to compromise psychological and emotional well-being, and recent research reported that 38% of lower-risk MDS patients suffer from anxiety and depression, a significantly higher proportion than age-matched healthy controls (Stauder et al., 2018). Depression has consistently reported to be highly correlated with fatigue in

cancer patients (Wang and Woodruff, 2015), and fatigue is considered an important symptom of clinical depression (McAuley et al., 2010). The causal relationship between depression and fatigue is unclear. For example, whether fatigue causes patients to become depressed, or whether patients become fatigued because they are depressed, is not fully understood (Brown and Kroenke, 2009). Nevertheless, the well-established relationship between psychosocial factors and fatigue in cancer patients highlights the requirement for subjective assessments when determining factors which contribute to fatigue in MDS. Thus, to provide further insight into the contributors to fatigue in MDS, studies should include comprehensive assessments of patient-reported outcomes such as depressive symptomatology, insomnia severity, social provisions and emotional well-being.

Treatment-related complications

As discussed earlier, RBC transfusion therapy is a common treatment option which aims to reduce anemia and anemia-related symptoms. Although transfusion is essential in order to manage anemia in non-responders or relapsed responders to ESAs, complications and side effects can occur in transfusion-dependent patients (Castelli et al., 2018). There are two primary adverse effects of transfusion-dependency with potential implications for chronic fatigue. Firstly, transfusional iron-overload is one of the most common negative implications of transfusion-dependency, with studies demonstrating that 81% of regularly transfused patients exhibited iron-overload in the liver and 16.8% in the heart (Roy et al., 2011). Iron-overload occurs due to infusion of RBCs containing high concentrations of iron, much of which is unexcretable due to a lack of regulated elimination mechanisms for excess iron (Baron et al., 2020). Under normal conditions, free iron released from hemolyzed RBCs is rapidly sequestered by transferrin. However, during transfusion of one unit of RBCs, 60 mL

of damaged RBCs (damaged through storage lesions, discussed later) are removed within 24 h, with iron subsequently released (Dumont and AuBuchon, 2008). As only 1 mL of RBCs per hour are removed under normal physiological conditions, transfusion can overwhelm both the reticuloendothelial system (involved in extravascular uptake of iron by macrophages) and the capacity of transferrin (Yoshida et al., 2019). Once the transferrin-binding capacity is exceeded, non-transferrin-bound iron (NTBI) accumulates (Gattermann, 2018). In turn, the increase in NTBI causes macrophages in the blood vessel wall to accumulate iron, leading to increased production of ROS, decreased efflux of cholesterol, and damage to endothelial tissue. Secondly, in addition to iron-overload, another adverse effect of transfusion dependency is RBC storage-induced damage, termed "storage lesions". When RBCs are removed from the circulation and stored hypothermically in blood banks, storage lesions can accumulate through various purported mechanisms (Yoshida et al., 2019). In turn, the transfusion of RBCs subject to storage lesions can have numerous negative physiological and clinical consequences (Kaphan et al., 2019). Physiologically, damaged, non-viable RBCs are removed *in vivo* through hemolysis or eryptosis, with an increase in the proportion of removed cells with storage duration (Baron et al., 2020; Rapido et al., 2017). The removed RBCs subsequently release their contents, causing an increase in free iron leading to the negative physiological consequences of increased NTBI previously discussed. Moreover, intravascular hemolysis causes an increase in free hemoglobin, which scavenges NO, causing insufficient NO bioavailability and subsequent negative effects on endothelial function. Thus, in addition to other deleterious clinical consequences of iron-overload and RBC storage lesions (Gattermann, 2018; Kaphan et al., 2019), the damage to endothelial tissue and increase in NO scavenging associated with these events can impair endothelial function.

The negative effects of iron overload and storage lesions could plausibly be an aggregator towards chronic fatigue in MDS. Indeed, fatigue is a common symptom associated with iron-

overload, with liver iron concentrations associated with fatigue in patients with genetic hemochromatosis (Adams et al., 1997). Although the mechanisms by which iron-overload induces fatigue are unclear, several factors could be responsible. For example, if iron-overload and RBC storage lesions induces impairments in endothelial function as previously described, this could in turn negatively impact the ability to deliver and utilize oxygen in skeletal muscle, thus exacerbating metabolic stress during activities of daily living. In addition, iron-overload could contribute to increases in inflammation and oxidative stress which have previously been associated with fatigue in MDS patients (Meyers et al., 2005). An interesting area of research is thus to examine iron-overload and the clinical consequences (e.g. endothelial function, oxidative stress and NO metabolism) of iron-overload in MDS patients, and explore the relationship between these factors and chronic fatigue.

Potential role of physical activity interventions in reducing chronic fatigue in Myelodysplastic Syndromes

The present review highlights the numerous potential physiological and psychosocial contributors to fatigue in MDS. Examining these mechanisms and their relationship with fatigue can assist in devising strategies to reduce fatigue, and thereby improve HRQoL, as is one of the primary treatment aims in MDS, particularly in lower risk patients (Fenaux et al., 2019). Taking the above-mentioned mechanisms into account, one non-pharmacological intervention which warrants investigation regarding its effect on fatigue is physical activity. Indeed, in other cancer types, exercise interventions have displayed efficacy in reducing many of the above-mentioned mechanisms, including inflammation (Gleeson et al., 2011), oxidative stress (Repka and Hayward, 2016), vascular and (Beaudry et al., 2018) physical function (Jones et al., 2011), sleep quality (Fang et al., 2019) and HRQoL (Mishra et al.,

2012). In MDS, only one study has investigated the feasibility of implementing exercise interventions. In their pilot study, Schuler *et al.* (2016) examined the effect of a 12-week home-based exercise program consisting of endurance and strength training exercise on alternating days in 21 patients with low- to intermediate-2-risk MDS. The study demonstrated feasibility of the physical exercise program, as evidenced by more than 50% of patients completing the program (Schuler *et al.*, 2016). Improvements in patient functional capacity were also displayed through an improvement in the distance covered in a 6-minute walking distance (6-MWD) test, though no significant effect on fatigue was noted. Importantly, the study reported no adverse effects to the exercise program, supporting the safety of this approach (Schuler *et al.*, 2016). Similarly, another pilot study on the effect of a 12-week home-based exercise training program in 40 patients with AML demonstrated successful recruitment, good retention and no adverse effects of the training program (Alibhai *et al.*, 2014). Accordingly, these studies have demonstrated the feasibility of safety of exercise training interventions in patients with MDS, thereby paving the way for future research in this area.

CONCLUSIONS

Chronic fatigue is the most common, severe and debilitating symptom in patients with MDS, and has widespread implications which ultimately lead to a reduced HRQoL. This notwithstanding, the aetiology of chronic fatigue in this patient group is incompletely understood. While the majority of MDS patients have anemia, a hallmark symptom of which is fatigue, the available evidence on the effects of interventions which mitigate anemia in MDS patients is equivocal regarding the effects on fatigue. Moreover, cross-sectional research has indicated that the relationship between Hb levels and fatigue is weak to

moderate, at best. Consequently, given that one of the primary aims of treatment, particularly in lower-risk MDS patients, is to improve HRQoL, understanding the factors contributing to chronic fatigue is an important area of research. The present review provides several potential aetiologic agents relevant to chronic fatigue in MDS which can be used to guide further research.

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Conflict of interest

All authors had no conflicts of interest

Table and Figure legends

Figure 1. Illustration showing potential contributors to chronic fatigue in myelodysplastic syndromes (MDS). Anemia is the most common objective manifestation of MDS, with fatigue a hallmark symptom of anemia (Efficace et al., 2015a). While anemia likely explains, to some degree, chronic fatigue in MDS, the association between hemoglobin (Hb) and fatigue is weak (Efficace et al., 2015a; Jansen et al., 2003) or non-existent (Steensma et al., 2008), and fatigue often persists even after anemia is temporarily ameliorated through various treatments (Casadevall et al., 2004; Spiriti et al., 2005). Consequently, understanding other potential contributors to chronic fatigue in MDS is necessary. A number of other physiological abnormalities are present in MDS, such as inflammatory dysregulation and higher levels of inflammatory markers including TNF- α , IL-1 and IL-6 (Shi et al., 2019), all of which have been associated with fatigue in MDS (Meyers et al., 2005). Mechanistically plausible links also exist between oxidative stress, which is elevated in MDS (Saigo et al., 2011) and chronic fatigue, as well as impaired vascular function and oxidative stress resulting from transfusion-induced iron overload and storage lesions (Gattermann, 2018; Kaphan et al., 2019). Moreover, anemia, inflammation and oxidative stress are also associated with impaired muscle size, strength and contractility (Cesari et al., 2004; Cheng et al., 2016; Reid and Moylan, 2011). All these factors can further influence levels of fatigability, potentially

leading to the accumulation of fatigue and/or the avoidance of physical activity, thereby contributing to further physical deconditioning.

Table 1. Results from studies exploring the relationship between hemoglobin concentrations and chronic fatigue in myelodysplastic syndrome (MDS) patients.

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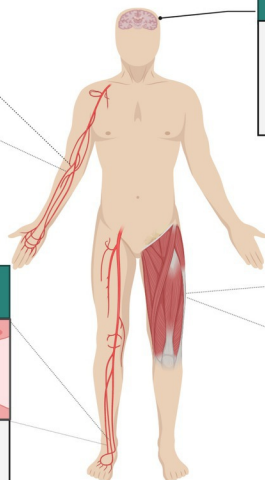
Anaemia, inflammation and oxidative stress



- Anaemia highly prevalent in MDS (Castelli, *et al* 2018; de Swart, *et al* 2015)
- Increased levels of inflammatory markers linked with fatigue (e.g. TNF- α , IL-1, IL-6; Shi, *et al* 2019)
- Heightened oxidative stress markers in 85% of MDS patients (Saigo, *et al* 2011)

Psychosocial factors

- Depression and anxiety high in MDS patients (Stauder, *et al* 2018)
- Sleep disorders common in MDS (Luskin, *et al* 2017), particularly among fatigued patients (Efficace, *et al* 2015a)

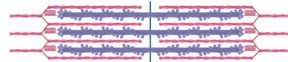


Impaired endothelial and vascular function



Iron overload prevalent amongst regularly transfused patients (Gatterman, 2018) with potential subsequent effects on endothelial function and vascular responsiveness (Duffy, *et al* 2001)

Muscle size and contractility



- Anaemia associated decrements in muscle size and strength (Caseri, *et al* 2004)
- Inflammation and oxidative stress associated impairments in muscle contractility (Cheng, *et al* 2016; Reid, 2008)

Increased fatigability and impaired muscle strength

