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Adverse neuropsychological effects associated with cumulative doses of corticosteroids to treat childhood acute lymphoblastic leukemia: A literature review

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ABSTRACT

Corticosteroids (CS) are an essential component of childhood acute lymphoblastic leukemia treatments (cALL). Although there is evidence that daily doses of CS can have neuropsychological effects, few studies have investigated the role of cumulative doses of CS in short- and long-term neuropsychological effects in cALL. The aims of this review were to identify the measures used for documenting adverse neuropsychological effects (ANEs) of CS treatment and to study the association between cumulative doses of CS and the presence of ANEs. Twenty-two articles met the inclusion criteria. A variety of measures were used to evaluate outcomes in the domains of emotion, behaviour, neurocognition, and fatigue/sleep.

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The results suggest that we cannot conclude in favour of an association between the cumulative dosage of CS and ANEs. Yet, several factors including the heterogeneity of measures used to evaluate outcomes and reporting biases may limit the scope of the results. We offer several recommendations that could help improve the future published evidence on ANEs in relation to CS treatment in cALL.

1. Introduction

Childhood acute lymphoblastic leukemia (cALL) is the most prevalent cancer among children (Ward et al., 2014). The survival rate has increased dramatically over the past few decades and has reached up to 90% (Brown et al., 1999; Canadian Cancer Society, 2008). However, this success has been possible at a high cost for patients. Large studies have reported a wide array of late effects in this population, including significantly more frequent cognitive, emotional and behavioural difficulties when compared to healthy controls or siblings (Buizer et al., 2005; Elalfy et al., 2014; Felder-Puig et al., 2007; Gordijn et al., 2012). Studies identified subgroup of cALL survivors which report more large-scale deficits in quality of life (de Vries et al., 2008; Eiser et al., 2006). While several factors may contribute to these difficulties such as female gender, younger age at diagnosis, cranial irradiation and overall treatment intensity (Buizer et al., 2005; Drigan et al., 1992; Edelstein et al., 2011; Waber et al., 2012; Armstrong et al., 2007). Researchers have also hypothesized that the intense use of corticosteroids (CS) in current treatment protocols for cALL may be influencing some of the behavioural outcomes (Elalfy et al., 2014; Felder-Puig et al., 2007; de Vries et al., 2008; Eiser et al., 2006; Drigan et al., 1992; Edelmann et al., 2013; Hochhauser et al., 2005; Marcoux et al., 2012; McGrath and Pitcher, 2002; Mrakotsky et al., 2011; Pound et al., 2012a; van Litsenburg et al., 2011). In comparison to other late effects, these neuropsychological late effects have been relatively understudied and their associations with treatment characteristics are still poorly understood. In the present study, we focused on specific adverse neuropsychological effects: emotional, behavioural, cognitive, and fatigue/sleep difficulties.

CS are an essential component of the main cALL treatment protocols (BFM, COG, DCOG, DFCI, UKALL, etc.). They are administered during the induction phase, the delayed intensification/consolidation phase, and the maintenance/continuation phase (Children's Oncology Group, 2011; Goldberg et al., 2003). Prednisone (PRED) was originally the most common CS used in ALL protocols but has gradually been replaced by dexamethasone (DEX), as it yields a higher event-free survival at a prednisone (mg)/dexamethasone (mg) dose ratio less than seven (Inaba and Pui, 2010a). Studies have compared PRED and DEX on neuropsychological outcomes in the past decade, leading to contradictory results (Felder-Puig et al., 2007; Eiser et al., 2006; Edelmann et al., 2013; Bostrom et al., 2003; Kadan-Lottick et al., 2009; Mitchell et al., 2005; Waber et al., 2013). DEX was traditionally suspected to cause more adverse neuropsychological effects (ANEs) due to its higher blood-brain barrier penetration (Edelmann et al., 2013; Marcoux et al., 2012; Inaba and Pui, 2010a; Stuart et al., 2005). In contrast, a recent systematic literature review did not find any clinically significant differences between PRED and DEX on cognition, mood or behaviour during and after treatments (Warris et al., 2014). Interestingly, there has not yet been any attempt to synthesize knowledge on the effect of the dosage of CS on adverse behavioural outcomes in cALL.

The mechanisms underlying steroid-induced ANEs are still largely unknown (Inaba and Pui, 2010a; Stuart et al., 2005; Marcoux et al., 2013; Warrington and Bostwick, 2006; Judd et al., 2014). Studies have suggested the imbalance hypothesis between mineralocorticoid receptors and glucocorticoid receptors activated in the HPA axis, as one of the explanation of the neuropsychological impact of intense CS treatments (Judd et al., 2014; Joëls et al., 2008; de Kloet et al., 2007). During therapy, there is clear evidence suggesting a relationship between current dosage, duration of treatment and the occurrence of steroid-induced adverse effects. This has been demonstrated in prospective cohort studies in cancer and other conditions requiring intense use of CS such as rheumatoid arthritis and lung disease (Inaba and Pui, 2010a; Kadan-Lottick et al., 2009; Huscher et al., 2009; Kayani and Shanon, 2002; Walsh et al., 2001). One study evaluating adults with inflammatory rheumatic disease distinguished two types of dose-related patterns (Huscher et al., 2009): a "linear pattern" in which the frequency of adverse effects increased linearly with dosage, and a "threshold pattern" in which adverse effects are observed over 7.5 mg/day, during at least six months of CS treatment. In this study, sleep disturbances followed a linear relationship whereas depression or apathy followed a threshold pattern (Huscher et al., 2009). In children with asthma treated over five days, it was shown that anxiety and aggressiveness were more frequent in a group receiving 2 mg/kg daily compared to 1 mg/kg (Kayani and Shanon, 2002). Regarding long-term effects, however, limited evidence is available.

In line with these observations, efforts have been made to assess differences between DEX and PRED on neuropsychological outcomes. A recent review showed that randomized controlled trials with neuropsychological function as the primary or secondary outcome did not show clinically significant differences between DEX and PRED regarding their effects on cognition, mood or behaviour (Warris et al., 2014). However, the purpose of this review was not to examine the association between dosage and ANEs. In other conditions, studies have shown that ANEs could be associated with *daily* dosages during active CS therapy (Inaba and Pui, 2010a; Huscher et al., 2009; Walsh et al., 2001). But in cALL, data on associations between *cumulative* dosage of CS and the frequency of ANEs have not been integrated thus far.

The aims of this review were to identify measures used for documenting ANEs and to synthesize the associations between the cumulative dosage of CS and the occurrence of ANEs in children treated for cALL. As neuropsychological outcomes and measures may be highly heterogeneous, we compared studies finding support for ANEs with studies finding no support for such effects in their reported cumulative dose of CS. As suggested by previous reports on ANEs in cALL, effects on the domains of emotion, behaviour, neurocognition as well as fatigue/sleep are broadly defined ANEs. As time is an essential factor when reporting adverse effects, we divided results into two categories: on-treatment effects among patients of cALL, and off-treatment effects among survivors. Studies supporting the association between CS and neuropsychological outcomes were either those finding significant differences on outcomes between on- and off-CS treatment, or those finding significant differences when comparing with baseline measures, or when comparing with population norms (i.e., scores above the validated clinical cut-off points on domains of emotion, behaviour, neurocognition, and fatigue/sleep).