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Vincristine-induced peripheral neuropathy in children with cancer: A systematic review

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ABSTRACT

Vincristine-induced peripheral neuropathy (VIPN) is a dose-limiting side effect of vincristine (VCR) treatment in children, leading to diminished quality of life. Much remains unknown about the underlying mechanisms of VIPN. This review systematically summarizes the available literature concerning contributing factors of VIPN development in children. Studied factors include patient characteristics, VCR dose, administration method, pharmacokinetics, and genetic factors. Furthermore, this review reports on currently available tools to assess VIPN in children. In total, twenty-eight publications were included. Results indicate that Caucasian race, higher VCR dose, older age and low clearance negatively influence VIPN, although results regarding the latter two factors were rather conflicting. Moreover, genetic pathways influencing VIPN were identified. Furthermore, the studied tools to assess VIPN seriously impairs comparability across study results. Studying the factors and their interactions that seem to influence VIPN in children, should aid in personalized VCR treatment, thereby increasing VCR effectiveness while minimizing toxicity.

1. Introduction

Since the introduction of vincristine (VCR) in 1962 has it been used as a chemotherapeutic agent in the treatment of various types of both adult and pediatric cancers. VCR is a vinca alka-

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loid derived from the plant *Catharanthus roseus* (Stearn, 1975). It causes restriction of tumor growth through its interference with the microtubules in the mitotic spindle (Coccia et al., 2012; Stryckmans et al., 1973). The main side effect of VCR is neurotoxicity: a dose-limiting side effect causing peripheral and mostly symmetric sensory-motor neuropathy (Jain et al., 2014; Vainionpaa, 1993; Purser and Johnston, 2014). Other side effects of VCR include syndrome of inappropriate antidiuretic hormone secretion (Escuro et al., 1992; Tsujita et al., 1998; Palomar et al., 1979; Philip et al., 1979), myelosuppression (Haggard et al., 1968; Carbone et al., 1963) and alopecia (Haggard et al., 1968; Carbone et al., 1963). Clinical symptoms of VCR-induced peripheral neuropathy (VIPN) include muscle weakness, areflexia, neuropathic pain and sensory loss, amongst others. Furthermore, it can cause autonomic polyneuropathy resulting in symptoms such as orthostatic hypotension and constipation.

In VIPN-affected patients the longer neurons such as the more distal neurons in the (lower) limbs are mainly affected (Gutierrez-Gutierrez et al., 2010; Gomber et al., 2010; Windebank and Grisold, 2008; Beijers et al., 2012; Anghelescu et al., 2011). The symptoms of VIPN often develop already after a few administrations of VCR and in most cases symptoms disappear a few months after discontinuation of VCR therapy (Sandler et al., 1969). However, some children experience long-term sequelae, clinically established by symptoms such as permanent loss of deep tendon reflexes (DTR) and decreased motor functions (Vainionpaa, 1993; Hartman et al., 2008).

In order to thoroughly study the influence of several factors on VIPN, it is important to use valid and reliable assessment tools.

In clinical practice the diagnosis of VIPN is hard to establish due to its heterogenic clinical presentation. Moreover, for young children it is difficult to describe their complaints, which is information necessary to accurately diagnose VIPN. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) are frequently used for assessing the degree of VIPN. This tool assesses the severity of several types of adverse events (National Institutes of Health, 2010). However, it has been demonstrated that the CTCAE has floor- and ceiling effects when it comes to assessing VIPN (Gilchrist et al., 2014). As a consequence, other methods to assess VIPN have been studied (Gilchrist et al., 2014; Gilchrist and Tanner, 2013; Lavoie Smith et al., 2013; Gilchrist et al., 2009). Currently, no golden standard is available to assess VIPN and most of the tools used have limited value in young children, making it difficult to accurately quantify VIPN in this group of patients (Gilchrist and Tanner, 2013). Another method used to diagnose VIPN as well as to elucidate the possible pathophysiology of peripheral nerve damage is electrodiagnostic testing (Vainionpaa et al., 1995; Courtemanche et al., 2015). This method, however, is more invasive and painful which makes it not suitable for routine assessment of VIPN in children.

The mechanisms underlying VIPN have been studied frequently. However, most studies included adults only. As a consequence, there is a gap of knowledge about the various factors that influence VIPN in children. Moreover, results of previous studies regarding the relation between VIPN and age seem to be contradictory (Jain et al., 2014; Vainionpaa, 1993; Lombardi et al., 2015; Diouf et al., 2015; Lavoie Smith et al., 2015; Kojima et al., 2011). Also the exact role of VCR pharmacokinetics (PK) on VIPN in children remains to be established (Egbelakin et al., 2011; Moore et al., 2011).

The development and severity of VIPN in children is determined by multiple factors which often are inter-related (see Fig. 1). One of these factors is the VCR dose administered. Standard dosing in children nowadays is 1.5–2.0 mg/m^2 with a maximum of 2.0–2.5 mg, and in infants the dose is 0.05–0.065 mg/kg. Furthermore, in general, VCR is administered with a minimum interval of one week (Gidding et al., 1999a). Larger doses or smaller time intervals may result in unacceptable toxicity (Diouf et al., 2015). However, this toxicity can also be the result of interactions with other drugs. The most frequently studied interaction is that of VCR and azole antifungals. Multiple publications showed increased VIPN after concomitant azole therapy (Moriyama et al., 2012; van Schie et al., 2011; Baxter et al., 2011). Furthermore, the method of administration seems to affect VIPN development and severity (Verstappen et al., 2005). In clinical practice, VCR is administered intravenously through bolus injections or prolonged infusions. Gidding et al. have shown that VCR bolus injections induce high peak-plasma concentrations of VCR, which in turn seems to be related to the development of VIPN in children (Gidding et al., 2001). In addition, continuous infusion of VCR seems to increase the systemic exposure of VCR without significantly increasing the development of VIPN (Kellie et al., 2004). However, strong evidence from high-quality studies is lacking.

Another factor influencing the risk of developing VIPN concerns the patients' PK profile (Egbelakin et al., 2011). Since the early nineties, high performance liquid chromatography (HPLC) with sensitive detection limits has become the standard method for most of the PK studies due to which accurate data on PK measures of VCR have become available (Gidding et al., 1999a). Although these data have demonstrated large inter-individual variability in children (Gidding et al., 1999b), studies indicate that in general VCR plasma clearance is higher in children than in adults (De Graaf et al., 1995; Crom et al., 1994). Since high clearance of VCR is associated with diminished drug exposure (Kellie et al., 2004), this may lower the risk of developing VIPN. However, genetic factors also influence this risk, either through influencing the PK of VCR or through genetically increased susceptibility of developing VIPN (Diouf et al., 2015; Gidding et al., 1999b). Several abnormalities in DNA such as single nucleotide polymorphisms (SNPs) with different pathways have been studied in VIPN-affected children (Diouf et al., 2015; Egbelakin et al., 2011; Plasschaert et al., 2004). Genetic factors influence the development of VIPN by altering the clearance on one hand and by influencing the patients' susceptibility for developing VIPN on the other hand (Diouf et al., 2015).

All in all, many factors influence the development of VIPN in children. However, results of previous studies investigating the exact impact of each of these factors on VIPN as well as the relation between these factors and VIPN are inconclusive, making it difficult to unravel the rather complex mechanism(s) underlying VIPN in children. This review aims to systematically summarize the available evidence concerning the various factors that contribute to the development of VIPN in children. Factors that are being studied include VCR dose, administration method, PK and genetic factors. Furthermore, this review reports on the psychometric qualities of the current available tools to assess and diagnose VIPN in children.

2. Methods

A review protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)-statement (www.prisma-statement.org). Subsequently, a literature search was performed using MEDLINE/PubMed (from 1945 up to December 13th 2016) and EMBASE/Ovid (from 1980 up to December 13th 2016). The following key words were used: "pediatrics"; "vincristine" and "neurotoxicity". The exact search queries for the literature searches in the several databases are stated in Supplementary Table 1.

Publications were deemed eligible for inclusion in case they met the following inclusion criteria: (a) study population: study should include a pediatric oncology population consisting of at least five children, (b) treatment protocol: children should have received multiple VCR administrations, (c) study measurements: