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Pediatric chemotherapy induced peripheral neuropathy: A systematic review of current knowledge

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ABSTRACT

Background: The dramatic increase in the number of childhood cancer survivors over the last 60 years has made monitoring and minimising long term side effects of cancer treatment increasingly important. Chemotherapy induced peripheral neuropathy (CIPN) has been described with many commonly used chemotherapy agents. This article provides a critical overview of pediatric CIPN, its incidence, clinical manifestations, late effects, and recent advances in understanding of risk factors and pharmacogenomics as well as evaluating current assessment strategies and treatment approaches.
Methods: Neurotoxicity data was systematically collated from Medline, Embase and Pubmed and analysed for quality, relevance and originality in three stages prior to inclusion. Quality scoring was done using the QUALSYST assessment tool.
Results: A total of 61 studies met inclusion criteria. Peripheral neuropathy is common and may be long lasting with characteristics specific to each chemotherapy agent. There is significant variability in reported incidence and natural history, related to challenges in clinical assessment and diagnosis. Emerging risk factors for CIPN include treatment factors such as dose, duration and concurrent medication and patient factors such as age and inherited susceptibilities. Recent identification of individual genetic variations has advanced understanding of pathomechanisms and may direct future treatment approaches.
Conclusion: While these studies guide suggestions for current clinical practice, further systematic research with development of strategies for amelioration and prevention of CIPN is necessary. Standardised assessment protocols and objective outcomes measures of CIPN applicable to patients of different ages are critical to enabling the development of novel treatments and facilitation of future clinical trials and treatment individualisation.

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Introduction

There has been a steady increase in incidence of childhood cancer diagnoses in developed countries since the 1950 s and a concurrent decline in mortality with the overall five-year childhood cancer survival reaching 80% for nearly all cancer types [1]. Accordingly, there is now a burgeoning population of childhood cancer survivors, with an estimated 388,500 long term survivors in the United States alone [2]. It is, therefore, critical to characterise the long lasting side effects of treatment for childhood cancer, as well as accurately assess, monitor and ultimately develop management strategies to prevent persistent treatment related side-effects.

Many chemotherapy agents used in cancer treatment can cause acute and chronic peripheral nervous system injury and dysfunction termed 'chemotherapy induced peripheral neuropathy' (CIPN). Peripheral nerve toxicity has been described with vinca alkaloids, platinum compounds, taxanes, epothilones, bortezomib and thalidomide. Vinca alkaloids and platinum compounds are the more commonly used agents in childhood cancer and the efficacy and tolerability of several of the other agents is being investigated. Individual chemotherapy agents are known to produce a broadly reproducible pattern of CIPN affecting the sensory, motor and/or autonomic components of the peripheral nervous system [3].

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The purpose of this review is to guide current management and future translational research by providing an evidence base of our current understanding of CIPN in children and childhood cancer survivors, pediatric-specific assessment and diagnostic strategies and any available treatment approaches.

Methods

Search strategy and selection criteria

This review was undertaken according to the PRISMA guideline for systematic reviews. All published scientific literature on pediatric CIPN was considered for inclusion with the most recent database search performed on 18 February 2016. We searched Medline, Embase and Pubmed for articles using the terms 'peripheral nervous system diseases', 'peripheral nerve injury', 'neurotoxicity syndromes', 'peripheral neurotoxicity', 'peripheral neuropathy' or 'toxic neuropathy' as subject headings or key words, in conjunction with each chemotherapy agent. This was limited to children aged 0–18 years or to specific age ranges including preschool children (1–6 years), children (6–12 years) or adolescents (13–18 years). Articles from the authors' database and bibliographic references cited by original and review articles identified as part of the literature search were also explored and cross-referenced against the search results.

An awareness of the relative scarcity of information on pediatric CIPN has led to the design of broad inclusion criteria for this systematic review. The studies were analysed in three stages prior to inclusion in the final review. Case reports, case series, original research articles or systematic reviews published in the English language were appraised in more detail if they had adequate data on CIPN as an assessment or outcome measure, included a minimum of 25% pediatric or adolescent ($\leqslant$18 years) patients or survivors of childhood cancer in the study population. Animal or basic science research articles, conference abstracts and studies utilising chemotherapy regimens with more than one neurotoxic agent were excluded.

Data extraction and analysis

Original research articles thus identified were scored using the QUALSYST assessment tool [4], a standardised system which gives a score between 0 and 2 for aspects of study design, selection and description of subject and comparison group characteristics, randomisation and blinding where relevant, description of exposure and outcome measures, sample size, statistical analysis, reporting of results and control for confounding factors. The total score out of a possible 28 is then converted into a standardised score out of 1.

Data on the type and topic of the research study, sample size, neurotoxic agent, details and limitations in assessment and reporting of peripheral neurotoxicity as well as the score on each individual QUALSYST item was extracted and recorded in a spreadsheet by TK. A QUALSYST cut-off score of 0.55 was chosen in order to capture 75% of the articles as well as ensure inclusion of several descriptive articles which contained valuable data on clinical characteristics of agent-specific neuropathy. Following quality scoring, the final selection of articles was reviewed by all authors and inclusion was on the basis of originality and relevance (Fig. 1 and Appendix A).

Data synthesis

The studies were categorised based on chemotherapy agent and whether they assessed neurotoxicity during acute treatment or long term outcomes.

For each agent, further data regarding acute and long term clinical characteristics of neuropathy, electrophysiological changes and pre-disposing risk factors such as age, concomitant administration of other medications and dose-toxicity relationships were collated. The synthesis of the collective data for each agent involved classifying its reliability according to Strength of Recommendation Taxonomy (SORT) criteria (Level A-consistent and good-quality patient-oriented evidence, Level B-inconsistent or limited-quality patient-oriented evidence, Level C-consensus, usual practice, opinion, disease-oriented evidence or case series) [5]. In addition, the methods of neurotoxicity assessment that were utilised in these studies have been reported as these are likely to have an impact on the results, particularly in different pediatric age groups.

Results

A total of 1580 articles were identified and following removal of duplicates and application of initial filters, 209 records were examined in greater detail. QUALSYST scoring was carried out on 81 research articles that were not excluded for other reasons as detailed in Fig. 1. The median QUALSYST score was 0.8 (Range 0.17–1.00; IQR 0.65–0.89). Case series and case reports were considered separately and not scored using this tool. 61 articles were included in this review for the final qualitative synthesis. This comprised 3 randomised controlled trials, 6 prospective, 9 retrospective and 14 cross-sectional studies, 22 phase I and II clinical trials, 6 case series and 1 case report. These studies form the basis for the following analysis of clinical features, objective assessment and risk factors.

Agent specific peripheral neurotoxicity during treatment

Vincristine neurotoxicity was reported in 52% of the studies while only 5% reported on cisplatin neurotoxicity. 80% of the articles studied neurotoxicity during acute treatment and 20% reported on late effects (Table 1). Details of the individual agents are provided in Table 2 and summarised below.

Vinca alkaloids

Vincristine treatment produces sensorimotor and autonomic neuropathies. Motor impairment is most prominent in children, manifesting as foot drop, ataxia, gait abnormalities and muscle weakness which can be asymmetric [6–9]. Sensory symptoms include parasthesiae and dysaesthesia. Constipation may occur with autonomic nerve involvement [6–8,10]. There is a universal reduction or absence of deep tendon reflexes [9,11]. Cranial neuropathies characterised by hoarse voice, ptosis and extra-ocular eye movement abnormalities and rarely optic neuropathy have also been reported [12,13]. Vincristine related nerve changes occur early during the course of treatment in children, frequently within the first month [8,11,14].

In a retrospective review of six large treatment trials including a total of 4567 patients [15], severe or disabling peripheral neurotoxicity (National Cancer Institute Common Terminology Criteria for Adverse Events – NCI-CTCAE grade 3 and 4) with vincristine was observed in 10% of patients receiving cumulative doses of 5–10 mg/m^2, with a significant increase involving 20–52% of patients administered 30 mg/m^2, suggesting a cumulative dose-toxicity relationship (Table 2). Neuropathy of any grade (NCI-CTCAE 1-4) affected 78–100% of patients treated with vincristine and neuropathic pain was seen in up to 35% [8,10,11,14].

Neurophysiological changes occur early in the course of the treatment with conventional nerve conduction studies demonstrating a motor or sensorimotor axonal neuropathy in >90% of

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