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RACP Foundation Research Awards

YEAR 1 PROGRESS REPORT

Project / Program Title		Chemotherapy-induced peripheral neuropathy in the pediatric population : risk factors, assessment strategies and functional outcomes
Name		Dr Tejaswi Kandula
Award Received		2016 RACP P&CHD NHMRC Award for Excellence
Report Date		14 February 2017
Chief Investigator / Supervisor		Professor Matthew Kiernan
Administering Institution		University of New South Wales (UNSW)
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	Finish Date:	1 February 2019

PROJECT SUMMARY

Significant improvements in cancer treatment over the last few decades have led to childhood and adolescent cancer survivor rates of 80% or more for many cancer types and the lifespan for many childhood cancer survivors is comparable to other persons of their age. Childhood cancer survivors are a growing section of the population with unique health needs. It is, therefore, important to recognise and minimise the long-lasting side effectsof cancer treatment.

Chemotherapy, the main component of treatment protocols for many childhood cancers, can cause peripheral nerve injury. This can result in disabling symptoms which can be long lasting with significant impact on long term independence and quality of life. Previous studies have demonstrated 20-30% of long term childhood cancer survivors can experience effects of chemotherapy related nerve injury.

This current project aims to provide a comprehensive evaluation of chemotherapy related nerve injury both during and after treatment. We will standardize sensitive ways of measuring nerve function in children and adolescents of different ages. This is the first study that will follow children throughout their treatment cycle with regular nerve assessments. This will provide a greater understanding of the mechanism of nerve injury and allow treatment modification and future research into nerve protection strategies

PROJECT AIMS / OBJECTIVES

1. To describe the incidence, natural history and pattern of axonal dysfunction in chemotherapy induced peripheral neuropathy (CIPN) in a cross sectional sample of long term survivors of childhood cancer

Participants recruited from the Kids Cancer Centre Long Term Follow-up Clinic at Sydney Children's Hospital, one of the largest follow up cohorts of long term childhood cancer survivors in Australia, with >200 patients seen each year. A cross-sectional study was undertaken and recruitment was completed recently. Each participant underwent a single comprehensive neurotoxicity assessment and data was also collected on demographic, cancer and chemotherapy characteristics.

2. To investigate the pathogenesis of development and progression of CIPN, as evidenced by axonal dysfunction and functional impairment, during prospective, longitudinal follow up of children receiving chemotherapy

Patients commencing vincristine therapy were recruited prospectively from Sydney Children 's Hospital and stratified according to cancer type, with assessments at baseline and longitudinally at pre-defined time points during their treatment. Follow-up will be for a minimum of one year. Clinical, functional and quality of life assessments are being carried out during routine clinic visits. Neurophysiologic assessment are carried out under general anaesthetic, in tandem with other procedures scheduled as part of their treatment (such as central line insertion, bone marrow aspirate and lumbar puncture).

3. To integrate data obtained from the cross sectional and prospective studies and develop risk profiles associated with lasting neurotoxicity.

By correlating data on risk factors such as age, dose, duration and type of chemotherapy with functional outcomes we will identify risk profiles associated with development of neuropathy. In addition, by comparing neurophysiologic data on patterns of axonal dysfunction during treatment with longitudinal functional outcomes, we aim to develop biomarkers for detection of early nerve injury, thus allowing treatment modification.

SIGNIFICANCE AND OUTCOMES

This is the first study looking at the longitudinal and cross-sectional acute and long-term outcomes of peripheral neuropathy in childhood cancer examining its evolution using novel neurophysiologic, clinical, functional and patient reported outcome measures in a standardised assessment protocol. Given the very limited data in the literature in this area, we expect this to provide a significant contribution to the understanding of chemotherapy induced peripheral neuropathy in children .

Patient recruitment has been in progress since April 2015 and was completed in December 2016. A total of 122 long term survivors of childhood cancer were tested as part of the cross-sectional study. Data collation and analysis has been conducted for this study and a manuscript for publication is currently being prepared.

For the prospective longitudinal follow up study, a total of 36 participants were recruited which easily fulfils the power requirements of the study. An average of 4-5 comprehensive assessments have been carried out for each of these participants during their chemotherapy treatment and further

longitudinal follow up is still underway for these participants.

Early data analysis suggests that there is evidence of long lasting chemotherapy induced peripheral neuropathy in 25-30% of participants who had received vincristine and a higher percentage who received cisplatin, both of which are neurotoxic chemotherapy agents that are commonly used in childhood cancer chemotherapy protocols. The evidence for peripheral neuropathy is demonstrable across all measures utilised including the clinical, functional, neurophysiological and patient reported outcome measures. The increasing number of long term childhood cancer survivors and the potential impact of CIPN on their long term productivity and

quality of life emphasises the need for understanding this long term morbidity in section of the population. The expected final outcomes of the proposed research are:

- Establishment of a sensitive and objective assessment protocol for measuring early nerve injury in children incorporating neurophysiologic and clinical parameters allowing monitoring and modification of treatment
- longitudinal follow up will provide information regarding onset and progression of CIPN relative to the treatment administered; Using novel neurophysiologic techniques, we will gain a greater understanding of the pathophysiological mechanisms underlying CIPN and identify links between patterns of axonal injury and long term functional outcome
- understanding of the disease burden will help with planning long term health care needs and requirements for monitoring in childhood cancer survivors
- define risk profiles, using various patient, disease and treatment characteristics, such that treatment protocols can be individualised
- Standardisation of assessment techniques will assist with future research into neuroprotection
- at a population level, the data will contribute towards directing health care resources into prevention and management of morbidity from CIPN

I have completed recruitment by the end of 2 years of this research project and ongoing follow up and data analysis will be undertaken in the final year of this PhD project. It is anticipated that the current research project will provide pilot data which will form the basis for future translational research in clinical trials.

PUBLICATIONS / PRESENTATIONS

Journal Publications:

Kandula T, Park S, Cohn R, Krishnan A, Farrar M. Pediatric chemotherapy induced peripheral neuropathy: A systematic review of current knowledge. Cancer Treat Rev 2016; 50 : 118-128. doi: 10.1016/j.ctrv.2016.09.005

Conference Abstracts:

Kandula T; Farrar M; Murray J; Goldstein D; Krishnan A; Park S, 2016, 'Subclinical peripheral neuropathy prior to chemotherapy in colorectal cancer patients - Myth or reality?', presented as a poster at ANZAN Biennial Clinical Neurophysiology Workshop, doi. org/10.1016/j.cl inph.2015.11 .029

Manuscripts currently awaiting peer review:

Kandula T, Farrar MA, Krishnan AV, Murray J, Goldstein D, Lin CSY, Kiernan MC, Park SB. Multimodal quantitative examination of nerve function in colorectal cancer patients prior to chemotherapy.

Kandula T, Farrar MA, Kiernan MC, Krishnan AV, Goldstein D, Horvath L, Grimison P, Boyle F, Baron-Hay S, Park SB. Neurophysiological assessment of chemotherapy-induced peripheral neuropathv.

Conference Presentations:

Kandula T; Park S; Kiernan MC; Mizrahi D; Carey K; Cohn R; Krishnan A; Farrar M, 'Long term outcomes and risk factors for chemotherapy induced peripheral neuropathy in the paediatric population', 14th International Child Neurology Congress, Amsterdam, 01 - 05 May 2016

This data has also been presented at local conferences and has been accepted for a platform presentation at the American Academy of Neurology conference in Boston, April 2017