Abstract (Abstract of 100-120 words (not included in the above word count)

Research advances has led to an increased survival for childhood cancer and importantly, recognition of the quality of that survivorship. Unfortunately, adult survivors of childhood cancers often suffer an array of adverse health related side-effects arising from necessary treatment. A highly prevalent complication that occurs many years after cessation of treatment, is the long-term alterations in sensory perception. This is typically presented as pain as a young adult, with the number of patients reporting pain becoming an indeterminate complication. Recent investigations present the development of rodent models that allow the exploration of causative factors that initiate childhood cancer survivorship pain. Here we provide an overview that highlights the significant burden that survivorship pain has upon paediatric cancer patients.

Keywords: pain, chemotherapy, neurodegeneration

Introduction

Progressive advancement of clinical trials for research, improvements in clinical diagnosis and adjuvant treatment for childhood cancer, as well as centralisation of care to specialist units, have led to marked improvements in survival rates of childhood cancer. As a result, 76% of childhood cancer patients now live 10 years or more following diagnosis. Following on from the improved rate of survivorship, focus has now turned to understanding and identifying adverse health complications that arise due to their cancer and/or treatment, which in turn impairs quality of life in childhood cancer patients[1].

Impact of Chemotherapy upon Childhood cancer survivors

Chemotherapy is a primary cancer treatment that is cytotoxic to rapidly dividing cells, and in most cases does not discriminate between cancer cells and healthy somatic cells. As a consequence, cancer treatment inherently impacts upon crucial physiological systems that are required to function correctly for normal everyday life, and crucially these effects are exerted during the normal developmental trajectory of the child. The impact of this is that large proportions of childhood cancer survivors suffer from a multitude of differing health related side-effects due to their cancer treatment (84%[2]). Typical complications include cognitive impairments, anxiety, depression, fatigue, loss of motor coordination and nephropathy[3]. A consequence of this, is that chemotherapy not only impacts upon physiological systems that are key to 'survival' but also impairs the highly refined developmental processes that will define the integrity and functionality of these systems into adulthood. Ultimately impairing function later in life. This is now recognised, with chemotherapy induced complications afflicting 70% of childhood cancer survivors [2]. An important consideration is that chemotherapy induced adverse health side effects, increase in prevalence in later life [1,2]). Indeed, 68% of childhood cancer patients whom are 5 to 14 years post cancer diagnosis describe suffering from a chronic condition. However, significantly this number increases to 77%, 85% and 88% at 15-24 years, 25-36 and 40-49 years post-diagnosis, respectively [2]. Furthermore, the severity of these side effects are increasingly associated with those patients that were exposed to chemotherapy at a young age. It is now apparent that a large proportion of adult childhood cancer survivors are suffering health complications many years after the cessations of treatment. For example, ~80% of childhood cancer patients suffer from cognitive impairment and fatigue in adulthood. These adverse health complications were found in childhood cancer survivors whom were diagnosed with cancer between 11 and 15 years old, with quality of life reported when these patients were 35 years of age old [3,4]. In many instances these complications may go undiagnosed or under-represented in many instances.

Chemotherapy induced pain in childhood cancer survivors

A wide range of cytotoxic agents are used to treat childhood cancer[5], these include Platinum based therapies used for treatment of malignant brain tumours, neuroblastoma, hepatoblastoma, osteosarcoma and germ cell tumour [6], whilst vincristine is widely used in both leukaemia and solid tumours[7]. As highlighted these treatments not only damage cancer but also other physiological systems. It is widely accepted in adult cancer patients that chemotherapy impacts upon the somatosensory nervous system, with chemotherapy induced sensory neuropathy highly prevalent in adult cancer patients (indeed, upto 90% of patients are adversely affected [8]). This is typically demonstrated through the onset of chronic pain accompanied by hallmarks of sensory neurodegeneration inclusive of intra-epidermal nerve fibre degeneration [9,10]. These adverse effects are principally associated with the extremities of patients limbs, and continue for many months or even years after treatment has stopped [8]. To date this has almost exclusively been investigated in adult cancer patients whom have undergone cancer treatment. With regards childhood cancer patients, there is evidence that platinum based chemotherapy is detrimental to the sensory nervous system[11]. Platinum based treatments in children under 5 years of age, damages hearing in approximately 50% of patients, with damaged auditory systems less prevalent in older patients (5% in patients older than 15yrs old) whom undergo the same treatment [6,12]. Incidently, in young patients there is a precedence for a delay in presentation of symptoms[6]. This can be greatly debilitating as impaired hearing impacts upon the individuals speech and language development. Consequently, impairing the childs development hinders academic achievement, whilst also impeding sociality due to difficulties in communication [6,12,13]. This highlights that the sensory nervous system is susceptible to damage from chemotherapy treatment as well as long lasting complications, with instances whereby symptoms may not present until later in life.

One of the biggest health burdens for society is pain [14] and unfortunately there is a great body of evidence now supporting that adult survivors of childhood cancer suffer from sensory complications in relation to pain development. Despite the understanding that chemotherapy leads to significant neurotoxicity in adults, this knowledge has not been applied to understanding how cancer treatments may impact upon the quality of survivorship in childhood cancer survivors. Until recently the effect that cancer treatment has upon the physiological systems responsible for modulating pain in childhood cancer patients has not been extensively investigated. It is now recognised that~50% Childhood cancer survivors attribute pain as an adverse side effect of their cancer treatment [11,15]. The onset of survivorship pain is attributable to platinum and vinca alkaloid based chemotherapy[16,17], frontline treatments for

childhood cancer. It is important to note, that the prevalence (8-68%) of pain in childhood cancer patients is presented many years after the cessation of treatment (typically depicted as 10-15 years post diagnosis [7,18]). In addition, cancer treatment associated pain is increasingly prevalent with increasing age [2], with childhood cancer survivors also more susceptible to dependence upon prescribed analgesia[11]. Furthermore, patients who were at higher risks of pain later in life were those children diagnosed with cancer at a younger age and therefore exposed to treatment at a younger age[11]. Unfortunately, a long-term adverse health affliction such as chronic pain greatly limits physical activity, therefore is detrimental to academic and societal experiences such as attending higher education or interacting with friendship groups. Childhood cancer survivors typically have poor academic performance in part this is likely due to debilitating effects of chronic impact of pain[11]. Chronic pain in these individuals is associated with increased levels of fatigue and sedate lifestyles as their ability to perform physical tasks is impaired [11]. As a consequence of this, societal isolation childhood cancer survivors also suffer mental health issues depicted by anxiety and depression which further enforces chronic pain[11].

This work highlights a potential unmet clinical need that requires further investigation. Furthermore, there are no condition-tailored analgesics available for childhood cancer survivors[19] as analgesia is predominantly ineffective and/or cause adverse side effects in the long-term. These difficulties arise due to analgesic management being based upon other neuropathic pain conditions[20] and a complete lack of understanding to what causes chronic pain in adult survivors of childhood cancers.

Mechanisms underlying childhood cancer survivorship pain

It is recognised that in humans as well as in rodent models, chemotherapy damages[21,22] and subsequently causes chronic pain[24,25]. However, the vast majority of research to date has focussed upon adult chemotherapy induced sensory neuropathy[8,26]. This has provided a level of mechanistic understanding of peripheral sensory nerve afferent degeneration [27,28] and peripheral sensory neuronal sensitisation [23]. Understanding the mechanisms by which chemotherapy treatment can impair paediatric cancer patient quality of life through the onset of pain complications has, however, remained elusive. Recent work by several groups has led to the development of rodent models [29,30] that allow researchers to investigate those mechanisms by which chemotherapy administered early in life, causes a delayed but lasting pain into adulthood. These tools provide researchers the facility to investigate key causative factors that contribute to the development of chemotherapy induced neuropathic pain in paediatric patients. In addition, providing a pre-clinical basis to allow evaluation of the efficacy

of current and novel analgesic approaches to provide an informed decision of which analgesia should be introduced as frontline treatments for paediatric patients.

The nociceptive neuroaxis and pain perception is still developing during infancy and greatly depends upon an infant's environmental stressors and experiences[31,32]. Noxious insults early in life (such as chemotherapy) lead to chronic pain manifesting later in life[29,32]. Furthermore, sensory nerves, particularly pain detecting C fibre nociceptors, become sensitised[33,34], with sensory neurons possessing the capacity to become 'primed' therefore remaining active for the long term[35]. Despite this, it is still unknown how cancer treatment during childhood can affect pain mechanisms and quality of life in adulthood. Administration of cisplatin[29] or vincristine[30] early in a young rodents life (in the first 2 weeks of a rodents life) leads to chronic pain manifesting in adulthood in these rodents when compared to age matched controls. These observations were not restricted to either gender [30]. Interestingly cisplatin induces both mechanical and heat hyperalgesia[29], whereas vincristine only leads to the development of mechanical hypersensitivity[30]. These alterations in nociceptive behavioural outcomes were associated with no chemotherapy induced impairment upon motor coordination[30]. Furthermore, the manifestation of chemotherapy induced neuropathic pain in adults is typically associated with the degeneration of primary sensory nerve fibres, depicted by slowing of sensory nerve conduction velocity and loss of intraepidermal sensory nerve fibre (IENF) innervations [21]. Schappacher et al. highlighted a comparable pathology in the vincristine induced childhood cancer survivorship pain model, with a loss of Protein Gene Product 9.5 (PGP9.5) positive sensory nerve fibre skin innervations in the vincristine treated group when compared to age matched controls[30]. Similarly, Hathway et al. also highlighted degeneration of the IENF profile in the cisplatin treated experimental group[29]. Interestingly these histological pathological features in the paediatric models were observed at time points shortly after administration of the chemotherapeutic agent. Importantly, Hathway et al also observed IENF morphology at the termination of the study when pain had become established. Here aberrant growth of IENF profiles were observed in the cisplatin treated animals[29]. This is of importance as aberrant sensory nerve fibre growth is a hallmark of peripheral sensory neuronal sensitisation and chronic pain [36,37], providing interesting outcomes by which pain may manifest in paediatric patients. To support this, further work by Schappacher et al. has interrogated sensory nervous system electrical activity and functionality[38]. Overall conduction velocity of C and A fibre afferents were unchanged, but early life treatment with vincristine induces dorsal root ganglia sensitisation. This was depicted by increased evoked discharge and spontaneous firing, but solely in large and medium sized DRG sensory neurons as well as lamina I spinal cord projection neurons. Whilst interestingly small diameter DRG sensory neurons displayed reduced levels of activity. These studies highlight how exposure

of chemotherapy to young individuals greatly impacts upon the structural and functionality of the sensory nervous system and alterations in pain perception.

Conclusion

Although there is still much to be learnt, our current understanding of survivorship pain in adult childhood cancer survivors has established the significance of this problem. There is now a clear realisation of the negative impact pain has upon the quality of survival. Furthermore, integral studies have begun to decipher the impact cancer treatment has upon paediatric patients in relation to somatosensory neurodegenerative processes and pain development. Such information provides clinicians with crucial information that needs to be considered when tailoring patient treatment to ultimately support patients ongoing quality of life.

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