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Literature Review

What are the long-term effects of treatment on survivors of childhood leukaemia? A review of the literature

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Abstract

Purpose: Key advances in cancer treatment have led to an increasing number of long-term cancer survivors. Knowledge of the long-term effects of cancer treatment on leukaemia survivors is to some degree limited. This article investigates the effects of the treatment of childhood leukaemia on the quality of life (QOL), the physical and the psychological wellbeing and general development of survivors. This article reviews current literature to examine existing gaps in knowledge and identify a potential focus of future research and clinical practice.

Materials and methods: Online systematic searching, along with historical searching took place in order to retrieve relevant primary research papers for the review. Strict inclusion and exclusion criteria were applied to the literature, to create a manageable amount of research papers.

Results: The extent of intellectual impairment among radiotherapy patients was significantly greater than those treated with chemotherapy only. Body composition, including endocrine function, is readily affected by cancer treatment. Early identification and interventions can greatly improve the QOL of survivors.

Conclusion: Further research into the effect of treatment modality on the extent of chronic effects, along with investigations into the needs of the whole family unit, is required. Future practice must take into account long-term implications while ensuring effective holistic care.

Keywords: follow up; late effects; leukaemia; paediatric; physical; psychosocial; quality of life; survival

INTRODUCTION

The development of effective paediatric cancer treatments has drastically improved survival rates.[1–4] An increase in 5-year survival from <5% in the 1950s, to >75% in 2004, indicates the progress made.[5] A consequence of these increased survival rates has been a subsequent research focus on the long-term effects of paediatric cancer[6,7] and an emphasis on prolonged monitoring and support of survivors to enable effective management of quality of life (QOL) issues.[8]

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Leukaemia is the most common malignancy in children[9] but with the introduction of enhanced treatment regimes, cure rates of almost 80% have been achieved for childhood acute lymphoblastic leukaemia (ALL).[10,11] Treatment for leukaemia can involve; chemotherapy, radiotherapy, bone marrow/stem cell transplants and steroids. Each modality has different implications for the future health and development of patients; therefore, the impact of each modality must be recognised, to enable well informed treatment decisions.[10] With the benefits of specific treatments being well established, the potential of long-term effects and their management need to be taken into account.

The volume of current research regarding the chronic health and psychological problems faced by survivors of childhood leukaemia is steadily increasing. This is due to the improvement in aforementioned survival rates, which enables a greater number of participants to be recruited into research studies.[4]

The previous lack of research participants reduced the opportunity for longitudinal research needed to establish true long-term issues.[12] As survival rates continue to improve, there will be increasing numbers of available participants for future research. Currently, the knowledge base is developing, and a variety of primary research papers are exploring this topic.[13–15]

This article aims to assess information on the chronic effects of treatment on childhood survivors of leukaemia. It will consider the physical, psychological and developmental effects of treatment and their management.

QOL

Survivors of childhood cancer are faced with multiple long-term effects which can greatly impact upon their QOL.[16] Around two-thirds of survivors experience at least one long-term problem, while a quarter face a severe or life threatening late effect.[17] A number of studies highlight the relationship between treatment modality, age at diagnosis and the extent of long-term problems.[13,15,18,19] Chronic side effects in young patients treated with cranial irradiation appear to be exacerbated, with there being fewer chronic side effects noted between chemotherapy regimes.[20]

With all cancer treatment there is the risk of acute and chronic side effects that may impact on a patient's QOL. Therefore, understanding the risks associated with cancer therapies is the first step in improving future care.[21–23]

METHODOLOGY

An online literature search was performed. Combinations of search terms were used within this search, with the aim of collating the most relevant and up to date research papers. Table 1 displays the chosen search terms used.

In order to retain a manageable selection of research papers to review, inclusion and exclusion criterion were applied; creating a volume of appropriate literature.

RESULTS

Physical effects

Endocrine system

The endocrine system is readily affected by cancer treatments, resulting in numerous long-term problems.[24] The extent of these problems appears to be directly related to the treatment modality, with endocrine problems rarely seen in those treated with chemotherapy only. In contrast, leukaemia patients treated with total body irradiation (TBI) and bone marrow transplants (BMT) often experience late endocrine disorders.[25] Severe growth hormone deficiency (GHD) was seen in

Table 1. *Brainstorm of search terms*

Childhood	Paediatric	Adolescent	Pre-pubertal	
Survivors	In remission	Post treatment	Disease-free	Leukaemia
Psychological	Psychosocial	Physical	Developmental	Chronic
Problems	Implications	Issues	Concerns	Effects

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50% of those treated with TBI and BMT, with 56% experiencing thyroid dysfunction (mainly hypothyroidism). Steffens et al.[25] also found that 40% of males had biological signs of altered spermatogenesis, with all of the females treated with TBI and BMT having ovarian failure. The majority of patients studied were on some form of hormone replacement therapy with the aim of improving QOL. Close long-term follow up, regarding endocrine function, is regarded as essential in ensuring survivors are well supported.[24–27]

Body composition

Ness et al.[28] found the percentage fat mass of leukaemia survivors was significantly higher than the expected norms, with percentage skeletal and lean body mass significantly lower. In contrast, Murphy et al.[29] also established there to be a significant difference in percentage fat mass between survivors and control subjects, but no difference in relation to treatment type. Body mass index (BMI) has been found to be significantly higher in female survivors when compared with both the expected norms, and control subjects.[30] Females treated with high dose cranial irradiation (10–20 Gy), at a young age were found to have a mean BMI increase of 0·41 units per year.[31] Male survivors also demonstrated higher BMIs indicating weight problems. However, male control subjects also displayed signs of being overweight[30]; therefore, the effect of cancer treatment on male survivors' body composition was not established.

In terms of bone mineral density (BMD), there were no differences between cases and controls, apart from lumbar spine bone density, which was significantly lower in survivors.[32] No difference in BMD was found between groups who received cranial irradiation, and those who did not.[32] This information, coupled with the BMI data, highlights the need for childhood survivors, especially female, to be given guidance on healthy lifestyles in the long term to reduce the occurrence of obesity.

Physical ability

As a result of higher percentage fat masses, and lower BMD in some cases, problems with mobility and strength have been detected. Knee extension strength in particular is significantly lower in leukaemia survivors than the expected norms and control groups tested.[33] As a result, survivors walked significantly shorter distances in 2 minutes, demonstrating their impaired mobility.[28] Cranial irradiation was found to reduce strength and mobility, particularly in female survivors. One explanation for reduced mobility could be the effect radiation treatment has on motor nerve conduction.[34] This study identified a significant difference regarding motor nerve conduction and lower extremities, resulting in limitations of ankle movements and distal muscle weakness. Survivors' balance was also affected by treatment somewhat, with one-third of patients unable to complete the most challenging task.[35] Balance problems became clear when vision was removed, and survivors were tested with uneven surfaces. These problems pose a potential threat to survivors in terms of physical activity.

Physical activity during childhood and adolescent years is very important due to its protective effect on body composition and overall general health.[36] Florin et al.[36] found survivors had significantly lower physical activity scores than current recommended standards; those treated with cranial irradiation (>20 Gy) being most affected. Jarfelt et al.[32] noted male survivors previously treated with cranial irradiation, especially with existing GHD, experienced much lower exercise capacities, with no differences seen between female groups. Both aerobic and anaerobic exercise capacity have been seen to be reduced in leukaemia survivors, along with self-reported cardio-pulmonary fitness levels.[28] This would seem to suggest that patient education and compliance in terms of physical activity could reduce the negative effects of cancer treatment on physical fitness and function. However, the subjects in the study by Heath, Ramzy and Donath,[3] met or exceeded national standards for physical activity, with the exception of three children out of 19.

Psychological and developmental effects

Cranial irradiation has been shown to increase the extent of neurocognitive impairment.[37]

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When compared with a chemotherapy only group, those previously treated with radiotherapy scored lower in tests for verbal intelligence quotient (IQ), attention and concentration ability, and memory. Spiegler et al.[20] noted survivors treated with radiation scored significantly lower in arithmetic and reading/comprehension tests, whereas differences in attention and intellect were not detected.[38] This suggests that prophylactic cranial irradiation increases the risk of survivors experiencing neuropsychological impairment, resulting in certain cognitive and intellectual deficits.[37] Reduced volumes of white matter correspond to a greater deficit in intelligence and academic achievement, as a result of both cranial irradiation, and chemotherapy to a lesser extent.[38]

With regards to patients treated with chemotherapy only; selective aspects of cognitive functioning are impaired, especially visual processing.[39] Intensified courses of chemotherapy have been seen to cause extensive deficits regarding attentional flexibility, and visuomotor control.[40] Those diagnosed at a younger age appear more likely to be affected by certain deficits; however, it is unclear as to whether this is as a result of a greater susceptibility to chemotherapy drugs.[41] Although chemotherapy appeared to have little consequences concerning intellectual functioning, two young patients out of 21 did show a decline of >10 IQ points. However, greater educational support has been shown to reduce these effects on a survivor's intellectual functioning, thus such interventions can be effective.[39]

Following the completion of the Strength and Difficulties Questionnaire for children, no statistically significant differences in psychosocial health were seen.[42] Link et al.[43] found there to be no differences in self-reported QOL, yet a significantly lower level of education was reached. Only 23% of survivors reached university level, in comparison to 55% of healthy controls. In contrast, Reinfjell et al.[44] concluded that there was a significantly lower health-related QOL among survivors of leukaemia when compared with healthy controls. Intellectual functioning was determined to be within the normal range, but lower than that of the control group. These differences in self-reported QOL and intellectual functioning need to be investigated further, to enable the early detection of indicators relating to a declination of psychosocial wellbeing from the norm.

With greater than two-thirds of children diagnosed with cancer achieving disease free survival, it is essential to be aware of the long-term effects which may arise.[45] Early detection and interventions can improve the QOL of both cancer survivors and their family by relieving pressures and reducing the extent of problems.[16] Where cure is the aim, it is also necessary that the potential chronic issues do not outweigh the advantages. Treatment modality does play a part in the chronic effects experienced, therefore treatment plans need to be discussed in depth to provide the best care for each patient.[46]

CONCLUSION

The majority of the research papers focused on survivors of ALL and did not include other types of leukaemia such as acute myeloid leukaemia and chronic myeloid leukaemia. These forms of leukaemia are rarer thus the research available is limited. Nevertheless, it is important to investigate whether differences exist between the long-term effects for the different types of leukaemia to determine the optimum post treatment care.

As a result of the critical analysis of this literature review, it is clear that childhood survivors of leukaemia face many chronic side effects that impact upon their QOL. This is currently an inevitable consequence of curative treatment received. This highlights the importance of long-term follow up, especially for those diagnosed at a young age.[45] There are clear relationships between the extent of chronic effects, and the treatment modality, with cranial irradiation and TBI causing greater impairments.[25] Further research into this area is required to enable health professionals to shape the treatment of paediatrics, with the aim of providing them with the best QOL possible. Future practice must be concerned with long-term QOL as well as curing the short-term problem.

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Conflicts of Interest

None.

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