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Review article

The role of total body irradiation (TBI) as a conditioning regime for paediatric acute lymphoblastic leukaemia: A discussion of the evidence

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ABSTRACT

Aim: The long term effects of TBI with children can be adverse and has resulted in a debate as to whether chemotherapy only based condition regimes could be used as an alternatives. The aim of this article is to critically evaluate the literature relating to the role of TBI as a conditioning regime in ALL in children, and if there are any alternatives to current practices or future developments.
Method: Key databases were searched for terms: conditioning regimes, transplantation, TBI, whole body radiation, systemic irradiation, stem cell transplantation, hematopoietic stem cell, and transplant conditioning.
Results: Thirteen research articles from a variety of publications and two guidance documents from several sources were uncovered for critical discussion.
Discussion/conclusion: There is little evidence for chemotherapy only regimes in paediatric ALL, but the practice continues. Modulating doses to improve homogeneity and use of IGRT could hold a future solution to reducing long-term toxicity and maintain the efficacy of irradiation.

Introduction

Leukaemia accounts for the most common of all paediatric malignancies within the United Kingdom (UK).[1] Acute Lymphoblastic Leukaemia (ALL) has a peak incidence between 2 and 5 years of age, with an improving 88% five-year survival rate.[2] Allogeneic stem cell transplantation (SCT) benefits patients with high-risk ALL, such as individuals with Philadelphia chromosome and those with a poor initial response to treatment.[3] Although prognosis has improved in recent decades there is a difference in outcome between the overall survival in girls and boys, with 73.4% for girls compared with 63.5% for boys.[4] The most common cause of treatment failure in paediatric ALL is relapse, occurring in approximately 15–20% of patients, and a combination of myeloablative Cyclophosphamide (Cy) and Total Body Irradiation (TBI) is part of the standard of conditioning regime treatment in all stages of relapse, but chemotherapy only regimes are currently being reviewed in trials.[5,11,12] TBI is defined as a specialist radiotherapy technique that is designed to deliver a uniform dose to the whole of a patient's body, and the purpose of the technique is to induce myelosuppression suitable for SCT.[6]

The National Cancer Survivorship Initiative, Living with and beyond cancer: Taking Action to Improve Outcomes document states that by 2021, there will be nearly 11,000 more adult survivors of childhood cancer.[7] It is imperative to consider that those who were treated for cancer as children or young adults can face long-term consequences of treatment, such as heart problems or secondary cancers, and this must now influence the choice of management for disease.[8]

The long term effects of TBI on children can be adverse, patients may experience growth and development issues, secondary malignancy and long term organ toxicity. These factors have resulted in examination of whether chemotherapy only based condition regimes for ALL could be used as an alternative to those using radiation.[9,11–13] The American College of Radiology (2011) suggest that TBI has certain unique properties that offer advantages over chemotherapy based regimes such as no sparing of sanctuary sites such as the testes or central nervous system, a homogenous dose regardless of blood supply, reduced resistance, and no issues of extrication or detoxification.[10] The aim of this paper is to critically

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discuss the literature relating to the current and future role of TBI as a preparative conditioning regime for ALL in children.

Methodology

For the purpose of this paper a broad ranging literature search was carried out on Medline, Embase, CINAHL, AMED, and Science Direct, uncovering a variety of sources relating to ALL and SCT in paediatrics. Hand searching for documents on The Center for International Blood and Marrow Transplant Research (CIBMTR) and European Bone Marrow Working Group (EBMWG) websites was also carried out to discover guidance documents in this area. Keywords and synonyms searched included: conditioning regimes, transplantation, TBI, whole body radiation, systemic irradiation, stem cell transplantation, hematopoietic stem cell, and transplant conditioning. Articles were reviewed and selected on the basis that only those relating to paediatric ALL could be used. Once suitable literature was reviewed, references within these articles and documents were then investigated to ensure as broad and inclusive a search as possible. The decision was taken to not include literature that was published over ten years ago and English language only articles were reviewed.

Results

Thirteen research articles from a variety of publications and two guidance documents from several sources were uncovered in the literature search. The search results were then analysed to formulate the outline for the discussion for this paper. The data revealed contrasting views and various applications of TBI in ALL, but randomised controlled trials indicated that long term survival is better with conditioning regimes containing TBI. The results indicate research currently being undertaken to refine current TBI techniques dose conformance to reduce overall long term toxicity.

Discussion

TBI V chemotherapy

Two recent trials comparing chemotherapy only myeloablative regimes with TBI were uncovered as part of this review.[11,12] A randomised trial conducted by Bunin et al. (2013) evaluated the outcome for children with ALL undergoing allogeneic SCT with either combination Busulfan (Bu) and Cy, or Cy and a TBI regimen of 12Gy in 6 fractions over 3 days.[11] The trial concluded that there was no significant difference between Bu and TBI for 43 patients who received SCT from related donors. However, for unrelated donors, event free survival (EFS) was 20% for the Bu arm and 57% for TBI at a medium follow-up of 43 months. Relapses were similar in both arms and, based on the findings, the study suggests that Bu and Cy is inferior to Cy and TBI. Participants had a median age of 8 years old with a confirmed diagnosis of ALL and were undergoing allogeneic SCT, but genetic phenotypes which could influence survival rates, such as Philadelphia Chromosome, were not indicated in the data. This study had an uneven sex distribution of 29 boys and 14 girls which could therefore influence results further, due to the disparities in survival amongst those of differing gender.

A larger trial with 95 participants conducted by Eroglu et al. (2013) carried out a direct comparison of Bu and Cy versus TBI and Cy as a conditioning regime for ALL. Median EFS was 4 months in the Bu and Cy arm, while it was 13 months in the TBI and Cy arm indicating that TBI and Cy conditioning regimes to be superior to the Bu and Cy regime.[12] The larger cohort of patients within this study indicates a higher degree of certainty, but there were some flaws within the methodology such as a lack of randomisation and omission in the data of the patients' remission statuses. The median age of participants was 25 years making it hard to draw direct comparison with other studies, but was deemed worthy of inclusion within this discussion as the ages ranged from 9 years old. Details of the TBI technique were limited to describing a 6 MV Photon Beam at extended FSD with a dose and fractionation of 12Gy in 8 fractions over 4 days.

It should be noted that the aforementioned studies, both took place in a single centre, and as such may have some inherent bias and variables that could affect the outcomes given the lack of randomisation. These studies contradict a retrospective analysis over a ten year period conducted by CIBMTR that found no difference between TBI containing and chemotherapy only conditioning regimes.[13] The study reviewed children who had myeloablative regimes for ALL, finding a total number of 38 patients with an average age of eight years. TBI and non-TBI containing conditioning regimes were reviewed and were found to have no effect on disease-free survival, with survival rates of 30% and 27% respectively.[13] Chemotherapy agents such as Bu and Cy were used, but the doses and fractionation of the TBI regimes were not discussed in detail other than declaring that total doses of 6–8Gy over multiple fractions were used, indicating a variation in technique and doses that are lower that the other studies reviewed in this paper. Although there is a lack of detail within this retrospective study its findings challenge the notion that TBI regimes are superior.

As TBI still remains the treatment of choice refinements in technique have been employed to attempt to reduce long term side effects and organ toxicity. All the clinical trials comparing TBI and chemotherapy only based regimes reviewed for this paper indicate benefits of TBI on overall survival, but have failed to indicate outcomes of long term survival or quality of life beyond five years, principally because the studies reviewed followed up patients at approximately three to four years post graft. Any long term side effects will only just start to manifest at this stage and may not become apparent until further childhood development ensues.

Effects of TBI

Borgmann-Staudt et al. (2010) discuss the effects of various conditioning regimes on fertility through a retrospective study analysis of patients treated between 2000 and 2005.[14] The study encompassed seven European cancer centres and reviewed the outcomes of 138 female and 206 male patients with a median age at follow-up of 19 years. The median age for transplantation was 13 years old. The study revealed that amongst the participants presenting at follow-up, 17% of 133 females and 31% of 190 males appeared to be fertile. Various conclusions of the study were drawn including an indication that in TBI doses above 4Gy can lead to irreversible infertility in males and chemotherapy regimes demonstrated no effect on fertility. However, a contrast was observed in females whereby chemotherapy regimes such as VP-16, Bu and Cy did lead to fertility impairment, concluding that chemotherapy agents were not associated with infertility in males but in females. The study provided some details of TBI doses that were wide ranging from 2 to 14.4Gy. Due to the variation of dose and fractionation between the seven centres, the quality of the data is questionable considering that the lowest recorded dose for TBI is below the fertility threshold of 4Gy, but nevertheless is a good example of long term effects on fertility in a reasonably large patient cohort.

Faraci et al. (2005) examined late effects of TBI in 42 children at ten years post SCT follow-up.[15] Cataracts were observed in 78% of patients, hypothyroidism in 12%, thyroid nodules in 60% and thyroid carcinoma was diagnosed in 14% of survivors. Females who received SCT after menarche developed temporary ovarian