



Review

Neurocognitive outcomes in long-term survivors of childhood acute lymphoblastic leukemia treated on contemporary treatment protocols: A systematic review



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ARTICLE INFO

Article history:

Received 21 January 2015

Received in revised form 6 March 2015

Accepted 13 March 2015

Available online 7 April 2015

Keywords:

Acute lymphoblastic leukemia

Cancer survivorship

Chemotherapy

Neurocognitive

Pediatric cancer

ABSTRACT

The intensified administration of chemotherapeutic drugs has gradually replaced cranial radiation therapy (CRT) for the treatment of childhood acute lymphoblastic leukemia (ALL). While CRT is often implicated in neurocognitive impairment in ALL survivors, there is a paucity of the literature that evaluates the persistence of neurocognitive deficits in long-term survivors of pediatric ALL who were treated with contemporary chemotherapy-only protocols. Results from this systematic review concurred to the probable cognitive-sparing effect of chemotherapy-based protocols over CRT in long-term survivors. However, coupled with multiple intrinsic and extrinsic factors, survivors who received chemotherapy treatment still suffered from apparent cognitive impairment, particularly in the attention and executive function domains. Notably, there is evidence to suggest that the late neurotoxic effect of methotrexate on survivors' neurocognitive performance may be dose-related. This review also recommends future pharmacokinetic, neuroimaging and genetic studies to illuminate the multifactorial nature of this subject matter and discusses the potential value of neurochemical, physiological, inflammatory and genetic markers for the prediction of susceptibility to neurocognitive impairment in long-term survivors of childhood ALL.

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1. Introduction

Acute lymphoblastic leukemia (ALL) is the most prevalent cancer of childhood and accounts for 26.8% of cancer diagnoses among children worldwide (Kaatsch, 2010). The historical use of cranial radiation therapy (CRT), followed by intensive chemotherapy treatment of the central nervous system, has resulted in a 5-year-event-free survival rate of approximately 80% in standard-risk ALL (Gaynon et al., 2010). However, it is widely reported that these ALL survivors often suffer from long-term neurocognitive deficits that have a negative impact on their health-related quality of life (HRQoL) and daily functioning (Speechley et al., 2006; Huang et al., 2013).

There has been a paradigm shift in the treatment strategy for ALL over the past two decades (Simone, 2006). Although initial success was obtained with prophylactic CRT, this approach was gradually replaced by contemporary ALL therapeutic protocols, which consist of intensified intravenous and intrathecal administration of chemotherapeutic drugs for standard risk patients (Pui et al., 2004; Simone, 2006; Pui et al., 2009). A recent clinical trial reported that with the elimination of CRT, chemotherapy-only treatment protocols for ALL have resulted in an unprecedented overall survival rate of 93.5% (Pui et al., 2009). Despite these promising results, patients who received contemporary treatments still experience a myriad of treatment-related adverse effects, such as osteonecrosis and cardiovascular and endocrine morbidity (Pui et al., 2009; Essig et al., 2014).

This systematic review focuses on neurocognitive outcomes associated with contemporary ALL protocols. Notably, patients treated on chemotherapy-only protocols are reported to display lower performance on direct measures of attention and processing speed by the end of therapy (Conklin et al., 2012). The frequency of these problems appears to be associated with age at diagnosis and gender of the child (Krappmann et al., 2007). Thus, existing studies have established that even with the omission of CRT, ALL patients do suffer from mild but evident cognitive changes during active chemotherapy treatment.

Despite these reported problems, there is a paucity of studies that explore the long-term persistence of neurocognitive problems associated with contemporary ALL protocols. In this review, long-term survivors are defined as patients who have survived 5 or more years since the diagnosis of ALL, or more than 2 years from the cessation of treatment (Landier et al., 2004; Feig et al., 2009). The majority of the survivorship research has focused on the delayed cognitive outcomes of CRT-based regimens, with robust studies of chemotherapy-only regimens clearly lacking. A recent study evaluated the late effects of chemotherapy in 556 CRT-naïve long-term ALL survivors who were treated more than 10 years prior to symptom assessment, selecting patients identified as low-risk on older therapeutic protocols (Essig et al., 2014). ALL survivors reported poorer overall functional status, even though their perceived neurocognitive deficits and mental health status did not differ from a matched non-cancer population (Essig et al., 2014). More clinical studies are needed to answer the question of whether contemporary protocols do preserve ALL survivors' neurocognitive function and are less likely to elicit adverse cognitive and behavioral late-effects.

In view of the limited literature on this subject, the objective of this systematic review is to gather current evidence on the persistence of neurocognitive late-effects of chemotherapy-only, contemporary treatment protocols on long-term survivors of childhood ALL. It is anticipated that the pooled results from existing studies will help consolidate the consistent evidence, identify controversial findings, and provide directions for future research.

2. Methods

The literature search was conducted using PubMed, Scopus and PsycInfo databases in September 2014, with the following combination of keywords: “acute lymphoblastic leukemia”, “childhood”, “pediatric”, “behavioral”, “psychological”, “neuropsychiatry”, “anxiety”, “fatigue”, “depression”, “cognition”, “neurocognitive”, “memory”, “attention”, “learning”, “executive function”, “processing speed”, “sleep”, “stress” and “emotional”.

A set of inclusion/exclusion criteria was established to select studies that (1) were published between the years 2000 and 2014, (2) were written in English, (3) focused on long-term survivors of childhood ALL, defined as those who were diagnosed with precursor B-cell ALL before the age of 21 years old and were at least 5 years post-diagnosis at the time of assessment or at least 2.5 years post-cessation of treatment (based on the assumption that standard ALL treatment protocols are typically completed within 2.5 years from diagnosis), (4) involved a cohort of survivors who received chemotherapy-only treatment for standard-risk ALL and had no history of CRT or hematopoietic stem cell transplant, and (5) used quantitative methods to evaluate the neurocognitive endpoints.

Studies were excluded if they were meta-analyses, reviews, commentaries or qualitative in nature; if they only included a pure cohort of non-ALL survivors and/or ALL survivors who received CRT without presenting any stratified analysis for the neurocognitive outcomes in chemotherapy-only treated survivors; and/or if they did not describe the fundamental methods of the quantitative research, such as data collection methods, analytic and/or reporting strategies. This review is limited to precursor B-cell ALL as it is the more common presentation (80–85%) of acute pediatric ALL as compared to mature B-cell ALL and T-cell ALL, and also to ensure some degree of homogeneity in the types of treatment received by the study populations. Studies that were published before the year 2000 were excluded based on the historical development of ALL treatment protocols. The administration of intrathecal chemotherapy drugs gradually replaced prophylactic CRT in the 1990s for low-risk ALL patients (Pui et al., 1995, 1998; COG, 2015). By late 1990s to early 2000s, clinicians from major international pediatric oncology groups started to adopt non-CRT chemotherapy-based protocols for standard- and high-risk patients as well (Pui, 2003; COG, 2015). Hence, this review included studies that were published in year 2000 or later to provide a current perspective on the contemporary treatment strategies for childhood ALL with a minimum of 5 years of follow-up.

The search was conducted at three sequential levels: (1) at the initial “title stage”, titles were screened to exclude studies that were clearly not related to main interests of this review; (2) at the “abstract stage”, abstracts of studies that passed the “title stage” were reviewed; and (3) at the final “full-text stage”, the manuscripts were examined to ensure that they fulfilled the inclusion/exclusion criteria. Data extraction and summary of study results were conducted by the investigators independently, and any disparities in the findings were reconciled.

Characteristics of the studies were systematically abstracted using a standard methodology. Specifically, information was abstracted on year of publication, study design, sample size, patient characteristics, neurocognitive domains assessed, and pertinent conclusions.

3. Results

The results of the literature search are depicted in Fig. 1. The search provided 1501 studies from the three databases, of which

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