Chapter 17
Late Effects in Pediatric Acute Lymphoblastic Leukemia

Motohiro Kato

Abstract Overall survival probability of pediatric acute lymphoblastic leukemia is currently 80–90%. Considering this dramatic improvement, it has become increasingly important to recognize the occurrence of long-term late effects. Severe late effects—including secondary malignant neoplasms, cardiotoxicity, osteonecrosis, neurocognitive sequelae, and infertility—affect quality of life of childhood leukemia survivors. Cooperative groups have provided essential information about the long-term effects, giving recommendations for long-term follow-up.

Keywords Secondary malignant neoplasms · Cardiotoxicity · Osteonecrosis Neurocognitive dysfunction

17.1 Introduction

In the past two decades, the survival probability of children with acute lymphoblastic leukemia (ALL) has dramatically improved up to 80–90%. Thus, consideration for quality of life status in survivors is as important as further reduction of relapse risk. In general, children can tolerate more intensive therapy than adults, but chemotherapy and irradiation during infancy and childhood potentially cause late effects [1–3], defined as physical or psychological problems that persist or develop after 5-year from leukemia treatment.

Numerous reports demonstrated that long-term survivors of childhood leukemia are at a risk of developing various late effects [1, 2], such as secondary malignant neoplasms (SMNs), organ dysfunction, growth retardation, and decreased fertility (Table 17.1). Childhood leukemia survivors also often face social and psychological barriers, including schooling and job problems. To minimize the risk for late effects, ALL therapy has evolved substantially over time, particularly with the elimination

M. Kato (✉)
Department of Transplantation and Cell Therapy, Children's Cancer Center, National Center for Child Health and Development, Setagaya-ku, Tokyo, Japan
e-mail: kato-mt@ncchd.go.jp

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Table 17.1 Late effects of pediatric acute lymphoblastic leukemia

Late effects	Risk factors
Secondary malignant neoplasms	Irradiation, alkylating agents, topoisomerase II inhibitors
Cardiotoxicity	High cumulative dose of anthracycline (≥250 mg/m^2 of doxorubicin equivalent), younger age at treatment (<5 years old)
Osteonecrosis	Steroid (dexamethasone), older age, female
Neurocognitive sequelae	Cranial irradiation, intrathecal therapy (>20 times)
Dental problem	Irradiation, busulfan, younger age
Infertility	Irradiation, busulfan, older age (female)

of prophylactic cranial irradiation and the risk-adjusted use of chemotherapy [4]. Long-term medical follow-up based on current knowledge of late effects is required to maintain survivors' health and quality of life [3, 5]. The long-term follow-up guidelines for childhood cancer survivors by the Children's Oncology Group are found in http://www.survivorshipguidelines.org/.

17.2 Secondary Malignant Neoplasms

SMNs are one of the most serious complications and leading causes of late mortality of childhood cancer survivors [5–7]. DNA-damaging effect of chemotherapeutic agents and irradiation causes secondary malignancies in ALL patients treated with these modalities [7, 8]. Strikingly, the risk of developing SMNs remains elevated for more than 20 years from end of treatment. To avoid SMNs, recent clinical trials challenged to eliminate cranial irradiation by replacing with intrathecal therapy, and it successfully reduced an incidence of secondary brain tumor less than 2% [3, 9, 10].

Therapy-related solid tumors have a strong association with irradiation. Follow-up screening and surveillance of brain tumors should be performed after cranial irradiation, and thyroid cancer is also observed after stem cell transplantation with total body irradiation. As SMNs, hematologic malignancies are also observed after leukemia treatment. "Therapy-related" leukemia is mainly myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML). Previous studies showed that alkylating agents such as cyclophosphamide caused MDS/AML associated with chromosome abnormality involving deletion of chromosomes 5 and/or 7, while MDS/AML induced by topoisomerase II inhibitor is frequently associated with *MLL* rearrangement [11].

Recently, several studies demonstrated importance of germline pathogenic variants in cancer-predisposing genes in pediatric cancer. Familial cancer history can be a risk factor for developing SMNs [12], suggesting that genetic susceptibility also confers prevalence of SMNs. Actually, a large-scale study reported that loss-of-function germline *TP53* variants increased a risk of second malignant neoplasms [13].

17.3 Cardiotoxicity

Anthracyclines are widely used anticancer agents, not limited to pediatric ALL, but these are well-known causes of late cardiomyopathy, caused by myocardial injury due to formation of free radicals. In childhood cancer survivors, the reported incidence of anthracycline-associated clinical heart failure (HF) has been as high as 2% by 20 years after treatment [14], and incidence continues to increase with extended follow-up [15].

High cumulative dose of anthracyclines is a strong risk factor for heart problems, and leukemia survivors with ≥250 mg/m^2 of doxorubicin or the equivalent doses of other anthracyclines should be followed by annual echocardiogram and electrocardiogram. Dexrazoxane has a cardioprotective effect against anthracycline-induced heart failure [16].

17.4 Osteonecrosis

Avascular necrosis (AVN) of bone is an important musculoskeletal complication affecting activity of daily life of leukemia survivors. The diagnosis of AVN should be confirmed by magnetic resonance imaging. Low grade AVN is asymptomatic which can be found only by MRI [17], but severe AVN causes pain, and surgical procedure including total joint replacement is required in the most severe cases [18].

AVN is caused by reduced blood supply to the bones, and the older age (≥10 years), female, and dexamethasone usage are the risk factor for developing osteonecrosis. Alternate-week dexamethasone during delayed intensification phases reduced the risk of AVN without increasing relapse risk for children of older age [19]. A genome-wide association study identified an association between osteonecrosis and inherited variants in genes encoding glutamate receptors [20].

17.5 Neurocognitive Sequelae

Typically, neurocognitive sequelae develop as a result of irradiation for the whole brain [21]. Previous studies showed that risk factors for this late effect is higher dose of irradiation, younger age, and concomitant use of intrathecal therapy [22]. Childhood ALL survivors have a greater likelihood of being placed in special education or learning programs than their siblings, but most are able to overcome these problems [23].

To avoid neurocognitive deficit and SMNs, recent regimens omit prophylactic irradiation; intensive intrathecal injection and high-dose methotrexate also potentially causes long-term neurocognitive deficits and neurobehavioral problems [24, 25]. Younger patients and females are risk factors for these late effects [26].

17.6 Infertility

Compared with their siblings, childhood cancer survivors had an increased risk of clinical infertility [27]. Irradiation and high cumulative dose of alkylating agents potentially cause permanent infertility of childhood leukemia survivors. Myeloablative irradiation (≥8 Gy) and busulfan (>8 mg/kg) were associated with infertility due to gonadal dysfunction, and more than 90% of infertility was reported [28]. Age at receiving transplantation seems to be important in determining gonadal dysfunction, 50% of prepubertal girls who received total body irradiation will enter puberty spontaneously and achieve menarche at a normal age [28].

17.7 Dental Sequelae

Dental abnormalities can also occur in childhood leukemia survivors. Risk factors for aberrant dental development are irradiation and alkylating agents. Especially, children who received hematopoietic stem cell transplantation at younger age had many disturbances in dental development [29]. Regular dental examination is required.

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