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Upfront Therapies and Downstream Effects: Navigating Late Effects in Childhood Cancer Survivors in the Current Era

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Abstract

Purpose of Review As survival rates of those diagnosed with childhood cancer improve over time, the number of long-term survivors continues to grow. Advances have not only been made in the upfront treatment of childhood cancer, but also in the identification and treatment of late complications that may arise as a result of the chemotherapy, radiotherapy, or surgical interventions required to provide a cure.

Recent Findings As new therapies emerge that are often more targeted to cancerous cells while sparing healthy tissues, the hope is that cure can be achieved without the same long-term side effects for survivors. However, much is unknown regarding how these novel interventions will impact patients in the years to come.

Summary It is critical that we continue to follow patients treated with new modalities in order to identify and treat the long-term complications that may arise in future childhood cancer survivors.

Keywords Childhood cancer · Late effects · Survivorship · Long-term complications · Novel therapy

Introduction

Remarkable advances have been made in the treatment of childhood cancer, where 5-year survival rates are now over 80% [1]. As these survival rates have improved over time, the population of childhood cancer survivors has steadily increased and is now expected to exceed 500,000 by the year 2020 [2, 3]. Numerous studies have demonstrated that achieving a cure does not come without a price in the future [4–6]. Chemotherapy, radiotherapy, and surgical interventions can

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all result in long-term, chronic conditions which can have an adverse impact on nearly every organ system [7, 8•]. A recent report from the Childhood Cancer Survivor Study (CCSS) found that over time and with more tailored treatment regimens, the number of childhood cancer survivors with severe chronic conditions has declined over time; however, the 20-year cumulative incidence of at least one grade 3–5 chronic condition remains significantly elevated at 27.5% in the most recent cohort of survivors (those treated between 1990 and 1999). Comparatively, in a sibling cohort from the CCSS, the rate of similar chronic conditions was 4.6% [9•].

The Children's Oncology Group (COG) has developed guidelines based on available evidence and expert opinion to guide clinicians caring for childhood cancer survivors in assessing for late effects of treatment based on prior therapy exposures [10•]. However, therapy for childhood cancer continues to evolve, with an emphasis on more tailored therapies with the potential for less long-term toxicity. With the development of novel therapies for different types of childhood cancers, it is notable that survivors may be at risk for chronic conditions related to their cancer treatment that are not yet known.

Therapeutic Advances and Potential Late Effects by Disease Type

Leukemia

Acute leukemia is the most common pediatric malignancy and accounts for one third of all pediatric cancer diagnoses [11]. In the USA, approximately 4000 children under 10 years of age are diagnosed with acute leukemia each year, 75% of these cases being acute lymphoblastic leukemia (ALL) and the remaining 25% are acute myeloid leukemia (AML) [11]. Over the past 70 years, improvements in survival rates have occurred as a result of central nervous system-directed therapy, advances in supportive care, and intensification of multi-agent chemotherapy treatment through cooperative group trials. The most recent successes have been attributed to refining treatments based on risk-based cytogenetics, treatment responses measured by minimal residual disease (MRD), and the development of targeted chemotherapeutic agents and immunotherapies [12, 13]. Current long-term survival rates are above 90% for ALL and between 60 and 70% for AML [12, 14]. Despite these significant improvements, patients who undergo leukemia treatment are still at risk for late effects such as late mortality, subsequent neoplasms (SN), and permanent organ damage resulting in neurological, cardiac, endocrine, bone, and social/psychological disorders [13, 15]. The therapeutic focus has now shifted towards targeted therapies and immunotherapeutic approaches in an effort to provide more effective treatment and minimize late effects for pediatric leukemia patients.

Traditional late effects related to chemotherapy affect many organ systems, and leukemia patients are still at risk for early mortality as a result [16]. SN including myelodysplastic syndrome, AML, breast cancer, melanoma, CNS tumors, non-Hodgkin lymphomas, and thyroid carcinomas can result from radiation, alkylating agents, anthracyclines, and etoposide [17, 18]. Neurocognitive late effects are common from intrathecal methotrexate and cytarabine, CNS-penetrating chemotherapy such as corticosteroids and high-dose methotrexate, and cranial radiation [15]. These effects include attention problems, impaired visual and motor function, and decreased processing speed and memory which affect their quality of life and academic achievements [15, 19]. Vincristine can also cause dose-dependent peripheral neuropathy [20]. Cardiotoxicity in the form of left ventricular systolic dysfunction, progressive cardiomyopathy, myocardial infarction, and heart valve abnormalities occur as a result of dose-dependent anthracycline therapy [21]. Endocrine effects such as growth hormone deficiency, hypothyroidism, adrenal insufficiency, gonadal dysfunction, premature ovarian failure, and decreased fertility can also occur as a result of cranial radiation and alkylating agents [15, 22, 23]. Cranial radiation and corticosteroids also impair skeletal growth and can lead to decreased bone mineral density and osteonecrosis [15, 24, 25].

Targeted agents in both AML and ALL have become the focus of treatment for pediatric leukemias; however, due to the lack of long-term follow up data, many of the late effects are unknown. In ALL, the addition of tyrosine kinase inhibitors (TKIs) such as imatinib to the treatment of Philadelphia-positive ALL (Ph + ALL) have improved 3-year event free survival (EFS) outcomes to 80% from 35% and has allowed many of these patients to avoid the long-term toxicities associated with hematopoietic stem cell transplant (HSCT) [26]. Based on promising adult data, the TKI sorafenib has been added to upfront treatment in children newly diagnosed with AML with *FLT3*-internal tandem duplication [27]. Toxicities associated with this class of medications include cardiac dysfunction, edema and effusions, impaired linear growth, thyroid dysfunction, and vascular events [28]. Patients with Ph-like ALL with *ABL* mutations (*ABL1, ABL2*) or JAK-STAT signaling pathway-activating fusions (*CRLF2*, *JAK2*, and *EPOR*) are usually treated with dasatinib (a TKI) or ruxolitinib (a *JAK* inhibitor), respectively [29, 30]. Ruxolitinib is currently being studied in pediatric ALL trials and the long-term effects remain unknown.

Antibody drug conjugates such as gemtuzumab ozogamicin for the treatment of AML and inotuzumab ozogamicin for the treatment of ALL targeting CD33 and CD22, respectively [31, 32], are also being used. These agents are associated with hepatic toxicity and sinusoidal obstructive syndrome [22].

T cell-based immunotherapies including bispecific antibodies and genetically engineered chimeric antigen receptor (CAR) T cells have shown promising results with excellent initial responses in relapsed and high-risk patients. Blinatumomab is a bispecific T cell engager (BiTE) antibody construct that directs CD3-positive T cell-mediated killing of CD19-positive leukemia cells and has demonstrated promising results in the relapsed/refractory ALL setting [33, 34]. The main toxicity of this medication class is neurotoxicity, cytokine release syndrome (CRS), and transient elevation of aminotransferases [33, 34]. Further studies are needed to identify the chronic and late effects associated with blinatumomab exposure.

CD19 CAR T cells are patient-derived T cells which are genetically engineered with an anti-CD19 domain connected to intracellular T cell signaling domains that allow the T cells to directly target and kill the CD19-expressing leukemia cells. Potential exists for life-long persistence of these CAR T cells [28]. Trials in relapsed pediatric ALL have shown complete remission rates > 80% [35–37]; however, identifying a CAR target in case of AML has been more challenging as AML blasts share antigens with hematopoietic stem cells which will cause irreversible bone marrow aplasia unless it is used as a bridge to bone marrow transplant [38•]. The most common acute toxicities associated with CAR T cells include cytokine release syndrome (CRS) and neurotoxicities. A known long-term effect is B cell aplasia which may require ongoing immunoglobulin replacement to minimize disease risk [28, 35].

Lymphoma

Hodgkin lymphoma (HL) has been one of the most significant success stories of cancer therapy with 5-year overall survival rates reaching 95% [39]. This has led to a burgeoning of studies focusing on the late effect profile of these survivors in the last three decades. In comparison, studies involving survivors of non-Hodgkin lymphoma (NHL) have been limited primarily due to the histologic heterogeneity and limited cohort sizes. Similar to all childhood cancer survivors, survivors of HL and NHL have been found to be at a higher risk of late mortality due to SN, cardiovascular sequalae, and pulmonary causes when compared with the age-, year-, and sex-matched US general population [40]. These survivors are also at a higher risk of developing severe or life-threatening chronic health conditions (HL: RR 10.2; 95% CI 8.3–12.5; NHL: RR 6.8; 95% CI 5.3–8.6) compared to sibling controls [5]. Recently, Bhakta and colleagues provided a more precise estimate and found that survivors of HL and NHL developed, on an average, 5.2 and 3.9 severe, life-threatening, or fatal conditions by the age of 50, respectively, compared to 2.25 for community controls [7]. Radiation, anthracyclines, and alkylators are known risk factors associated with late effects such as SN, cardiovascular sequalae, and infertility.

Similar to patients with leukemia, the focus has shifted towards reducing the treatment-related acute and long-term toxicities while maintaining antitumor efficacy. Recent analyses from the Childhood Cancer Survivor Study (CCSS) reported a significant decline in the use of chest radiotherapy and anthracyclines in patients with HL from 1970 to 1990, translating into reduction in cumulative incidence of severe/life-threatening conditions and late mortality, which is reassuring [9, 41•]. However, as newer targeted agents such as Brentuximab vidotin and Pembrolizumab are being increasingly used in patients with HL, and with a potential future use of CAR T cells in patients with NHL, it would be pivotal to maintain comprehensive, longitudinal follow-up with systematic evaluations to understand the late effects profile of these novel drugs.

Sarcomas

Sarcomas comprise a variety of disease entities in pediatrics, which can broadly be grouped into two categories: bone sarcomas and soft tissue sarcomas. The most common bone sarcomas in children and adolescents are osteosarcoma and Ewing sarcoma [42]. Soft tissue sarcomas include rhabdomyosarcoma (most common) and a variety of other rare tumors that can occur in extremity muscles, or within the abdomen [42]. Both bone sarcomas and soft tissue sarcomas are treated with a multimodal approach including surgery, chemotherapy, and/or radiation therapy [43, 44]. Because of the disease heterogeneity within the group of pediatric bone and soft tissue sarcomas, many different chemotherapy combinations are used. Sarcoma survivors will face a variety of late effects depending on their chemotherapy agents used.

The type of tumor and location determine the modalities of local control that is required for treatment. When possible, surgery is a major component of sarcoma therapy. In instances when the tumor location is not amenable to surgery, radiation is often utilized. Depending on surgery location, sarcoma patients face a variety of late effects due their surgeries. Treatment for extremity bone or soft tissue sarcomas may include a limb-salvage procedure, rotationplasty, or amputation [44]. The degree of functional outcomes impairment is affected by the type, extent, and location of the surgery. Lower extremity tumor surgeries have been demonstrated to lead to decreased range of motion, decreased strength, and lower exercise tolerance [45]. In a CCSS report, no differences in quality of life were noted between patients undergoing a limb salvage compared to those who underwent an amputation [46].

Soft tissue sarcomas also can arise anywhere in the body, and patients face unique long-term challenges based on tumor location. Survivors of pediatric head and neck rhabdomyosarcoma face hypoplasia of facial tissues requiring reconstructive surgery, poor dentition, impaired vision due to cataracts,

corneal changes and optic atrophy, and hearing loss [47]. Soft tissue sarcomas arising within the abdominal cavity that are amenable to surgical resection will result in long-term effects, based on the individual surgery that has been completed. There is limited literature that summarizes the long-term outcomes for this population as each surgery is unique.

When surgical resection alone is not feasible for complete local control in pediatric sarcomas, radiation is used alone or in combination with surgery. Long-term sequalae of radiation therapy are related to the area of the body that required radiation therapy. Survivors of extremity sarcomas treated with radiation are at risk of muscle atrophy, growth abnormalities, and impairment of mobility leading to decrease function [48]. There is also an increased risk of fractures within radiation site, and risk of development of SN [48]. Survivors who received radiation to the abdominal cavity face potential development of chronic liver toxicity, bowel adhesions, and small bowel obstructions [49]. Additionally, they face challenges with bone growth of the radiation field, which often leads to scoliosis [49].

Neuroblastoma

With current therapy, 5-year overall survival for high-risk neuroblastoma (NBL) is approaching 50% [50]. Those patients with high-risk disease continue to require multimodal therapy, including chemotherapy, surgery, autologous hematopoietic cell transplantation, radiotherapy, targeted biologic therapy, and occasionally radiolabeled iodine-metaiodobenzylguanidine (^{131}I-MIBG) therapy. The result of this treatment approach has improved cure rates, but with high risk for significant chronic health conditions. Many late effects are not necessarily unique to NBL survivors (e.g., hearing loss following platinum-based therapy, risk for SN due to radiation therapy), though some conditions are associated specifically with the intensive multimodal treatments used in this disease [51].

Late effects involving the endocrine system are often described in long-term survivors of NBL. Hypothyroidism is observed with an incidence of 37–50% [52, 53] following therapeutic [52] or diagnostic [53, 54] ^{123}I-MIBG. This occurs despite prophylactic potassium iodide pretreatment and exclusive of total body or thyroid radiation. ^{131}I-MIBG therapy is also implicated in ovarian failure [55] in the absence of other causes of hypogonadism (high-dose alkylator, radiation therapy). Sustained gonadal exposure to MIBG radiation emission from an abdominal/pelvic tumor or excreted drug in the urinary bladder are posited as mechanisms of injury. Multifactorial growth failure is also observed, occurring in 68% in a single site, 17-year NBL cohort [53]. Radiation therapy to the primary tumor and metastatic sites is also associated with decreased height velocity (median z-score at diagnosis to 9 years post-therapy, − 0.01 and − 1.08, respectively) [56]. Cis-retinoic acid therapy is also contributory, associated with advanced bone age and premature epiphyseal fusion [51, 57].

Pancreatic insufficiency is commonly observed when therapy includes abdominal radiation, as is often the case in patients diagnosed with high-risk NBL. In a cohort controlled for age, sex, race, income, health insurance, and BMI, NBL survivors who received abdominal radiation were 9.2 times more likely to develop diabetes mellitus than their siblings [58], notably higher than other cancers which also receive abdominal irradiation.

Like other childhood cancer survivors, neuroblastoma survivors are at higher risk for developing SNs. Renal cell carcinoma (RCC) occurs in approximately 1% of NBL survivors [50, 51]. NBL survivors carry the highest risk for secondary RCC among the primary CCSS diagnostic groups [51], with a standardized incidence ratio of 128 [50]. Thyroid carcinoma was also reported with a standardized incidence ratio of 12.4 [50]. Lastly, one third of high-risk NBL survivors will have mild/moderate chronic respiratory symptoms including cough, congestion, shortness of breath, and wheeze [59]. A cohort of six patients was also recently described who developed bronchiectasis 4 weeks to 5 years following busulfan and melphalan conditioning therapy for autologous transplant, [60] which may have contributed to the late pulmonary toxicity.

The more recent addition of dinutuximab to neuroblastoma therapy has resulted in a significant increase in overall survival for high-risk patients [61]. Although the acute toxicities of this therapy can be severe and are well-known, whether the use of this GD2 monoclonal antibody will result in any long-term implications for the NBL survivor is unknown.

CNS Tumors

Children with CNS tumors are at the highest risk of long-term morbidities among all cancer types. CNS tumors are also associated with the highest cancer mortality and reducing the treatment intensity, while achieving optimal survival outcome, is particularly challenging in this area. Characteristic morbidities associated with CNS tumors include neurocognitive deficit, endocrinopathies, hearing loss, seizure disorder, secondary or recurrent neoplasm, and pulmonary function deficit [7, 62, 63].

Sixty percent of survivors of CNS tumors do not achieve complete independence in adulthood secondary to neurocognitive deficit and neuro-musculoskeletal dysfunction [64]. Major factors affecting neurocognitive outcome are age of diagnosis, baseline IQ, extent and dose of radiation, and hydrocephalus [65–67]. Young children, especially those less than 3-years-old, are vulnerable to radiation-associated neurocognitive delay. Due to this, craniospinal irradiation (CSI) in this age group is strongly discouraged.

Young children with desmoplastic nodular medulloblastoma and medulloblastoma with extensive nodularity (DM/MBEN) that coincides with the SHH molecule subgroup have good outcome by surgery and chemotherapy treatment [68]. Another approach for this age group is delaying radiation therapy by preceding chemotherapy. An extensive molecular study identified approximately half of young children with SHH medulloblastoma are good candidates for the delayed radiation approach [69]. Non-metastatic WNT subgroup medulloblastoma have survival outcome higher than 90% and now multiple clinical trials are undergoing to see if the excellent survival outcome can be maintained with reduced CSI dose [70].

Proton beam radiation therapy can save adjacent organ exposure such as thyroid from CSI, pituitary and hypothalamus from intracranial focal radiation to reduce the risk of endocrine sequela [71]. Platinum-based therapy has been widely used in CNS tumor treatment and ototoxicity develops within a short time from the exposure. Close monitoring and dose modification or use of alternative agents are recommended. Amifostine and sodium thiosulfate have shown the effect to reduce the frequency of platinum-based chemotherapy related ototoxicity in CNS tumor and other cancers [72, 73].

Molecular targeted therapy has been increasingly used especially in low-grade glioma which represents 40% of CNS tumors such as BRAF and MEK inhibitors, and MAPK signaling pathway inhibitors [74, 75]. Because of the slow growing nature, low-grade glioma yields excellent survival outcomes but requires prolonged treatment leading to cumulative morbidities. Introducing molecular targeted therapy may change the future standard treatment in this entity. Unique profiles of adverse events associated with BRAF and MEK inhibitors involving skin and eyes require close monitoring [76]. Fortunately, these acute toxicities tend to improve by cessation or dose reduction of the offending agents. Squamous cell carcinoma and keratoacanthomas can develop with the use of BRAF inhibitors as early as several weeks from the start of therapy and require dermatology referral for treatment. Remote late effects of these molecular targeted agents are not yet described and highlight an area for further investigation.

Hematopoietic Stem Cell Transplantation

Among childhood cancer survivors (CCS), HSCT survivors are at significant risk for chronic conditions and late effects. Outcomes of HSCT have continuously improved over the past two decades, hence the importance to understand the unique long-term health effects associated with this treatment modality. This improvement in survival is the result of better donor selection, advances in conditioning regimens offered and in supportive therapy including prevention and management of graft versus host disease (GVHD).

Most of the studies describing the late effects of HSCT are retrospective studies, or questionnaire based, and in many cases involve both adult and pediatric HSCT survivors [77–79]. An analysis of patients with hematologic malignancies enrolled on the St. Jude Lifetime study found that HSCT survivors were more likely to develop severe, life-threatening conditions compared to patients with hematologic malignancies treated with conventional therapy [80]. In addition, they were at higher risk for developing SN, grades 3–4 cardiovascular and pulmonary conditions, and frail health. In a previous study out of the Bone Marrow Transplant Survivor Study (BMTSS) and the Childhood Cancer Survivor Study (CCSS), compared to CCSS survivors, BMTSS survivors were at almost four times higher risk to develop a severe or life-threatening condition, almost three times more likely to suffer from multiple conditions, four times more likely to develop functional impairment, and six times more likely to suffer from activity limitations [77].

Various unique exposures/risks in HSCT survivors such as the use of total body irradiation (TBI) or busulfan as part of the conditioning regimen, donor choice, prolonged use of immunosuppressants, and developing chronic graft versus host disease (GVHD) are associated with higher risk for specific organ involvement. For example, TBI exposure is associated with higher risks for SN [81], endocrine problems including hypothyroidism, infertility [82, 83], and cataracts [84]. Chronic GVHD is associated with a higher risk for developing cataracts [85], skin cancers, and oral/dental late effects. Pulmonary toxicities represent the second highest risk for death in HSCT survivors second to SN [40, 86]. Pre-transplant exposures such as chest radiation, conditioning regimens using busulfan or TBI, and post-transplant complications such as infections and GVHD have all been associated with a higher risk for both early and late pulmonary dysfunction [87–89].

Reduced intensity conditioning regimens (RIC) consist of lower doses and/or less intensive chemotherapy agents or radiotherapy doses. RIC is often associated with less acute toxicities and may be better tolerated, especially in the setting of other underlying comorbidities. It is thought that using these regimens may subsequently result in fewer late effects. A large study done by the Center for International Blood and Marrow Transplant Research (CIBMTR) looked at late effects in severe aplastic anemia survivors treated with HSCT and who received RIC. Despite the use of RIC, survivors remained at risk for development of late effects (13% of those transplanted with a matched unrelated donor had at least one identified late effect at 1-year post-HSCT) [90]. More studies are needed to compare outcomes and late effects in RIC vs. myeloablative regimens in childhood HSCT.

Prospective, accurately graded, longitudinal studies are needed to better understand and establish associations between various exposures and late and chronic effects after HSCT in

Table 1 Potential late effects in childhood cancer survivors based on disease type

Diagnosis	Common therapy/known late effects	Novel agents/known late effects
Leukemia	Intrathecal chemotherapy: neurotoxicity Cranial radiation: SN, neurotoxicity, and endocrine Steroids: bone health Anthracycline: cardiomyopathy Tyrosine kinase inhibitors: endocrine Alkylating agents: fertility Topoisomerase inhibitors and alkylating agents: SN	CART Cells: B cell aplasia BiTE: unknown Antibody-drug conjugates: liver dysfunction
Lymphoma	Radiation: SN, endocrine, pulmonary dysfunction Alkylating agents: fertility Bleomycin: pulmonary toxicity Steroids: bone health Anthracycline: cardiomyopathy	Monoclonal antibodies: unknown
Sarcoma	Anthracycline: cardiomyopathy Surgery: musculoskeletal Radiation: SN, endocrine, pulmonary dysfunction, strictures Topoisomerase Inhibitors and alkylating agents: SN	
CNS	Radiation: SN, neurotoxicity, musculoskeletal, and endocrine Surgery: seizures, visual/auditory impairment Platinum: ototoxicity, nephrotoxicity	Proton beam radiation: more targeted area at risk Molecular targeted agents: dermatology, SN
Neuroblastoma	Anthracycline: cardiomyopathy Platinum: ototoxicity, nephrotoxicity Surgery: strictures Radiation: SN, musculoskeletal, endocrine ^{131}I-MIBG: endocrine, including fertility Cis-retinoic acid: endocrine Busulfan: pulmonary toxicity	Monoclonal antibody: unknown
HSCT	TBI: Endocrinopathies and fertility issues, SN, pulmonary dysfunction, cataracts, neurocognitive decline, dental, and musculoskeletal problems Chronic GVHD: SN, cataracts, autoimmune disorders, pulmonary issues, osteoporosis, and low bone density Busulfan: pulmonary toxicity, cataracts, hypothyroidism, infertility, SN	CART cells: B cell aplasia Gene therapy: unknown

the modern era. Areas such as quality of life, neurocognitive and neuropsychological effects, and frailty in adult survivors after transplant during childhood have not been studied. Late effects of novel cellular therapeutic modalities often used in conjunction with HSCT, such as CAR T cell and gene therapy, remain to be described (Table 1).

Conclusion

The field of childhood cancer survivorship is very active and evolving. The use of novel therapies, including targeted therapies, has led to improved disease response and is believed to be associated with less acute toxicities in many cases. However, late and chronic effects of these novel therapies remain to be studied.

Consortia-based, multi-institutional prospective survivorship studies are being designed and integrated into many of the novel therapeutic trials. Independent survivorship studies are also being conceived to answer the biological and genetic questions associated with the development of late and chronic effects in childhood cancer survivors. There is a significant knowledge gap related to our understanding of individual risk factors, such as genetic predispositions, that make one survivor at higher risk than others to develop certain late effects such as secondary neoplasms or detrimental cardiovascular effects. Many areas such as neurocognitive outcomes, frailty, quality of life, and patient-reported outcomes have not been well studied and deserve further attention. With a growing population of childhood cancer survivors being treated in an era of evolving therapeutic modalities, it is essential that we continue to actively navigate the incidence of and potential for late effects in the childhood cancer survivor.

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Conflict of Interest Rachel Phelan has received compensation from Orchard Therapeutics for service on an advisory board.

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