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Children's Oncology Group's 2013 Blueprint for Research: Survivorship and Outcomes

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Abstract

Improvements in the treatment of childhood cancer have resulted in over 360,000 survivors of childhood cancer in the U.S.. There is now a heightened recognition of the need to reduce treatment-related sequelae and optimize the quality of life of children treated for cancer. Survivorship studies conducted in the cooperative group setting have provided us with important information on long-term intellectual function, organ toxicity, reproductive outcomes, second cancers, late mortality, and disparities in outcomes. Ongoing health education initiatives have helped standardize the follow-up care for childhood cancer survivors and facilitate the early transfer of health-related information to patients, families, and healthcare providers.

Keywords

Children's Oncology Group; Survivorship and Outcomes; Late Effects; Health-related Disparities; Long Term Follow-up Guidelines

INTRODUCTION

Improvements in diagnostic precision, therapy and supportive care have resulted in a growing population of cancer survivors. Overall five-year survival rates for children with cancer now exceed 80%, and nearly 75% will be living 10 years following diagnosis, resulting in over 360,000 individuals who are survivors of childhood cancer in the United States. [1] Thus, for most children diagnosed with cancer today, cure is a likely outcome. With this success has come a heightened recognition of the need to reduce treatment-related sequelae and optimize the quality of life (QOL) of children treated for cancer. Because of their young age at diagnosis and potential longevity, any delayed consequences of therapy are likely to have a significant impact on childhood cancer survivors' lives, as well as on society at large. A growing need therefore exists to promote health, prevent secondary disease, and ensure the social, psychological, and economic well-being of long-term cancer survivors.

Historically, childhood cancer survivorship studies conducted in the cooperative group setting have examined a broad spectrum of health-related outcomes, including intellectual function, growth, gonadal function and reproductive outcomes, second cancers, organ

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toxicity, and late mortality. As a result of these and other studies, efforts have been made to modify therapy to mitigate potential long-term complications. Examples of some of these modifications include reduction or elimination of radiation therapy in specific clinical situations; reduction in cumulative exposure to anthracyclines, alkylating agents and platinum, specifically to decrease adverse long-term outcomes in the areas of cardiopulmonary, endocrine, renal, neurosensory, and reproductive function, psychological health, and subsequent malignant neoplasms. [2,3]

Future studies conducted in the cooperative group setting will need to continue to focus on addressing key gaps in knowledge related to the pathogenesis of adverse outcomes as well as the causes of disparities in outcome, with the ultimate goal to reduce the long-term morbidity and mortality following treatment of childhood cancer, across all sociodemographic and clinical strata. In addition, studies will need to examine the role of genetic susceptibility in the development of health-related outcomes, identifying high risk populations that will benefit from targeted intervention strategies. The research findings from these studies will need to be integrated into ongoing health education initiatives that will facilitate the early transfer of knowledge and help standardize the follow-up care of childhood cancer survivors.

STATE OF THE FIELD

Outcomes Research: Burden of morbidity

While overall survival rates for children and adolescents with cancer have increased over time, this improvement in outcome is not enjoyed equally by all. [4] Studies using population-based public datasets such as Surveillance Epidemiology and End Results (SEER) have demonstrated that while the overall 5-year survival rates have increased significantly from 63% (1975–1979) to 79% (1995–1999) $p<0.001$, underrepresented minorities have poorer 5-year survival rates than their non-Hispanic white counterparts (74% [Hispanics], 73% [blacks] vs. 81% [non-Hispanic whites], $p<0.001$). [4,5] Elucidation of biological and psychosocial factors underlying racial and ethnic disparities is needed to guide interventions to improve treatment outcomes for these vulnerable groups. For those who achieve long-term survival, cancer and its treatment can contribute to the development of a spectrum of adverse health-related outcomes including premature death, second neoplasms, organ dysfunction (e.g., cardiopulmonary, gonadal), impaired growth and development, decreased fertility, impaired intellectual function, and overall reduced quality of life. [6] Several studies have described the burden of morbidity by quantifying the chronic medical problems experienced by this population. [7,8] These reports suggest that three in four survivors experience at least one chronic medical problem and more than one third experience a late effect that is severe or life-threatening; childhood cancer survivors have an 8-fold higher risk of reporting a severe chronic health condition, when compared with age- and sex-matched siblings. [9] These studies demonstrate quite conclusively that the implications of cure are not trivial, and that the burden of morbidity carried by childhood cancer survivors is quite substantial.

Biology of Late Effects: Genetic susceptibility and gene-environment interactions

For a given therapeutic exposure, marked heterogeneity exists in the prevalence and severity of many of the long-term adverse outcomes experienced by cancer survivors. There is emerging data to suggest that genetic susceptibility influences individual response to therapeutic exposures. [10–13]

Currently, there is an established mechanism for ongoing centralized adverse event reporting and biospecimen collection for key outcomes such as second malignant neoplasms, stroke, cardiomyopathy/ heart failure, and osteonecrosis). This process has allowed investigators to

use a variety of platforms to identify genetic polymorphisms that could alter metabolic pathways of therapeutic agents associated with specific adverse events. [14] Many of these genomic variables, when fully established, could advance understanding of the pathogenesis of therapy-related adverse outcomes, and facilitate implementation of targeted primary prevention strategies (individualized therapy in future cancer populations), as well as secondary prevention strategies (targeted screening, behavior modification, and chemoprevention in long-term survivors).

Health Education: Knowledge about past diagnosis and treatment

In children, cancer-related complications often do not become apparent until years following cancer treatment. Due to the delayed onset of many treatment-related adverse events, long-term survivors (and their health care providers) must be knowledgeable about their cancer treatment and its associated health risks to make informed decisions about their health and facilitate their self-advocacy during health care interactions. However, survivors often lack basic knowledge about their cancer health history. An investigation of childhood cancer survivors' knowledge about past cancer diagnosis and treatment demonstrated that only 35% understood that serious health problems could result from past treatment. [15] These data underscore knowledge deficits among survivors and the need for educational initiatives to increase awareness about cancer-related health risks, health screening and risk-reducing measures.

To facilitate early detection of late effects and access to interventions to preserve health, the COG developed risk-based, exposure-related guidelines (Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers; www.survivorshipguidelines.org) [6] specifically designed for follow-up care of patients who have completed treatment for pediatric malignancies. Patient education materials, known as "Health Links" accompany the guidelines, offering detailed information on guideline-specific topics in lay language in order to enhance health promotion in this population with specialized healthcare needs. These Guidelines are regularly updated and maintained by task forces within the Survivorship and Outcomes Committee of the COG, providing clinicians and survivors with current recommendations regarding screening of therapy-related late effects.

Infrastructure to Conduct Survivorship Research

The integrity of survivorship research depends on the quality of long-term follow-up. Loss of study participants over time may reduce study power and introduce bias. In fact, studies have shown that a large majority of patients enrolled onto legacy cooperative group studies are lost to follow-up >10 years after completion of their treatment. [16,17] For many studies that include important randomization questions seeking to minimize treatment-related morbidity, long-term follow-up is a necessary component of outcomes assessment. However, long-term follow-up of children poses unique challenges including special protections for minors, changes in names and family structure over time and the lifestyle changes and mobility that come with young adulthood. Therefore, most institutions treating children with cancer are unable to continue active follow-up of their patients long-term, often due to lack of the resources needed to do so effectively and efficiently.

In order to overcome these limitations, the COG Survivorship and Outcomes Committee developed the Long-term Follow-up Center (LTFC), providing a cost-effective mechanism for life-long follow-up of children treated on COG frontline therapeutic trials in order to: 1) develop a mechanism for tracking and retention of all patients enrolled on cooperative group clinical trials; and 2) obtain therapeutic exposure data for all of these patients. The LTFC performs annual follow-up with patients, utilizing a variety of techniques to maintain

currency of contact information, and employs other available resources to re-establish contact with patients (or their parents) when contact has been lost. The LTFC maintains up-to-date demographic and self/parent-reported health status information on each patient enrolled. This updated information can be utilized to assist participating institutions in accomplishing protocol-specific data collection. In addition, therapeutic exposures for each registered patient completing active therapy is collected and entered into a central database. These data can then be linked with patient outcomes, facilitating identification of important associations between specific therapeutic exposures and health-related outcomes. The establishment of the LTFC has, in turn, facilitated the development of the next generation of survivorship studies that will evaluate outcomes long after completion of childhood cancer therapy.

RECENT MAJOR FINDINGS

Health-related outcomes

Understanding the Ethnic and Racial Differences in Survival—Acute Lymphoblastic Leukemia (ALL) is the most common malignancy in childhood. [18] Although a majority of children enter remission after induction, 20% relapse within 5 years. [18] Furthermore, Hispanics have a significantly inferior outcome compared with non-Hispanic whites, a difference not entirely explained by traditional risk classifications (i.e., cell lineage, white count at presentation, age at diagnosis). [19] Durable remissions require a 2-year maintenance phase that includes oral mercaptopurine (MP). [20] While lack of adherence to oral MP have been reported in children with ALL [21–23] few studies have systematically evaluated the effect of medication adherence on treatment-related outcome. A recently completed study measured the adherence to oral MP in Hispanic and non-Hispanic white children receiving maintenance therapy for ALL, and examined sociodemographic determinants of adherence. [24] After adjusting for all relevant prognostic factors, non-adherent patients (adherence rate <95%) were 2.5 fold more likely to relapse (p=0.002) compared to adherent patients. Importantly, the association between Hispanic ethnicity and relapse (HR 2.6; p=0.02) became non-significant (HR 1.8; p=0.26) after adjusting for level of adherence. Efforts are under way to better understand the genetic and sociodemographic/cultural/behavioral underpinnings of differences in survival for childhood ALL, setting the stage for a comprehensive interventional study (ACCL1033) to improve adherence and thus mitigate these disparities in outcome.

Neuroblastoma has marked clinical heterogeneity and widely varying rates of cure depending on a range of clinical features at diagnosis and biologic characteristics of the tumor. [25] Modern, risk-based, tailored therapies have led to improved survival over time. [25] Until recently, little was known regarding the association between race/ethnicity and survival in children with neuroblastoma. Investigators examined the relation between tumor biology and survival in neuroblastoma, using data from 3,539 children enrolled on COG clinical trials between 2001 and 2009. [26] After adjusting for known clinical and biological features of disease, there was a higher prevalence of late-occurring relapse events among blacks compared with whites, suggesting that this population may be more resistant to chemotherapy than others. In contrast to ALL, oral medications are not a major component of neuroblastoma treatment. This has led to the development of studies aimed at understanding the reasons for these disparities, including racial/ethnic differences in drug metabolism of commonly used agents, and in disease biology.

Neuropsychological Outcomes—High-grade gliomas of the central nervous system (CNS) are characterized by poor treatment response and prognosis for long-term survival. [27] A recently published study investigated the neuropsychological, behavioral and QOL outcomes after treatment for high-grade gliomas. [28] Median length of follow-up was 15

years and median age at evaluation was 24 years. While survivors demonstrated intellectual functioning within the low-average range, visual memory and psychomotor processing speed were between the borderline and impaired ranges, respectively. Approximately 75% of patients reported overall QOL within or above normal limits for both physical and psychosocial domains. Non-hemispheric tumor location (midline or cerebellum), female sex, and younger age at treatment emerged as independent risk factors. These results serve as a benchmark for comparison with future pediatric high grade glioma studies, in addition to identifying at-risk cohorts for interventions to minimize effects. Importantly, this study has demonstrated that important survivorship questions can be answered >15 years after study enrollment, using extramural funds to leverage the existing resources of the COG.

Neurocognitive functioning in children with standard-risk ALL was assessed in a cohort of patients, where investigators evaluated the modifying effect of randomization to glucocorticoids (dexamethasone vs. prednisone) [29] or intrathecal therapy (methotrexate alone vs. triple intrathecal) [30] on long-term neurocognitive functioning. At a median follow-up of 6 years, there were no differences in neurocognitive outcomes between patients randomized to either formulation of glucocorticoids or intrathecal chemotherapy. Specifically, in the dexamethasone vs. prednisone comparison, there were no group differences in mean neurocognitive and academic performance scores or the parents' report of neurologic complications, psychotropic drug use, and special education. These results have provided ALL investigators with critical insight into the safety of these therapeutic agents.

QOL Following Treatment of Childhood Malignancy—Acute myelogenous leukemia (AML): Bone marrow transplant (BMT) has been an effective therapy for children and adolescents with AML, and has become the standard of care for many children with matched-sibling donors. [31] BMT may be associated with late effects, which adversely affect the QOL experienced by the survivors. [32] Patients diagnosed with AML at less than 21 years of age and alive at least 5 years were included in a study evaluating QOL and risk behaviors. With a mean length of follow-up of 15 years, patients who underwent allogeneic BMT were at an increased risk of having a poor QOL profile when compared to those treated with autologous BMT. [33] Multivariate regression analysis revealed female gender and low household income to be independent predictors of adverse QOL, and there were no apparent treatment-related exposures that modified this risk. [33]

Neuroblastoma: Platinum chemotherapy forms the backbone of most contemporary neuroblastoma therapy. However, the use of platinum agents is limited by the dose-dependent association between these agents and risk of ototoxicity; this risk is especially high in children treated at a young age such as those diagnosed with neuroblastoma. [34] With a mean follow-up of 11.1 years after neuroblastoma diagnosis, investigators reported >30% prevalence of hearing loss, attributed to high cumulative dose of cisplatinum. Importantly, hearing loss was associated with lower school functioning scores and poorer self-reported QOL. [35] This study was one of the first to comprehensively evaluate the impact of treatment-associated hearing loss on school performance and QOL long after completion of therapy. Information obtained from this study has provided important insight into the design of future platinum-based therapies for children with other malignancies such as medulloblastoma, osteosarcoma, and germ cell tumors, setting the stage for lifetime dose reduction, and closer monitoring for academic and QOL issues after treatment.

Biology of Late Effects

Anthracycline-related cardiomyopathy is a well-recognized complication of cancer treatment. [36] There is a clear dose-dependent increase in cardiomyopathy risk that is

modified by younger age at exposure and chest radiation. [36] However, doses as low as 150 mg/m^2 result in cardiomyopathy in some patients, suggesting a role for inter-individual variability in anthracycline pharmacodynamics. [37] Carbonyl reductases (CBRs) catalyze reduction of anthracyclines to cardiotoxic alcohol metabolites. [13] Polymorphisms in *CBR1* and *CBR3* influence synthesis of these metabolites. [38] Using a case-control design, investigators examined whether single nucleotide polymorphisms in *CBR1* (*CBR1* 1096G_A) and/or *CBR3* (*CBR3* V244M) modified the dose-dependent risk of anthracycline-related cardiomyopathy in childhood cancer survivors. [39] After adjusting for known predictors of anthracycline-related cardiomyopathy, homozygosity for the G allele in *CBR3* contributed to increased risk of cardiomyopathy even at the lowest exposures for patients homozygous for the *CBR3* G allele. [39] A subsequent study evaluating genetic modifiers of early- and late-occurring cardiotoxicity in a different cohort of childhood cancer survivors identified multiple variants of the *SLC28A3* gene as important modifiers of anthracycline-related cardiotoxicity risk. [40] Information obtained from these studies add to the emerging body of literature [13] that genetic susceptibility could play an important role in modifying risk of developing adverse health-related outcomes in survivors of childhood cancer. Importantly, these results will facilitate the development of enhanced surveillance and/or prevention strategies among survivors at increased risk of cardiomyopathy.

Health Education

Long-term Follow-up (LTFU) Guidelines—The COG-LTFU Guidelines are risk-based, exposure-related clinical practice guidelines intended to promote earlier detection of and intervention for complications that may potentially arise as a result of treatment for childhood cancers. [6] Implementation of these guidelines is intended to increase awareness of potential late effects and to standardize and enhance follow-up care provided to survivors of pediatric cancer throughout the lifespan. The LTFU Guidelines can be downloaded at www.survivorshipguidelines.org. These Guidelines undergo regular review and revisions, with extensive revisions compiled and collectively released as new Guideline versions every 5 years (most recently, Version 3.0, 2008), led by the collective effort of multidisciplinary taskforces. Multidisciplinary task forces consist of national experts, representing oncology, nursing, family practice, radiation oncology, the specific subspecialty, and patient advocacy. These task forces meet annually in order to review the Guidelines and provide annual updates. A Publications Committee coordinates and facilitates publications resulting from the Guidelines, thus enhancing dissemination.

Research activities pertaining to the COG-LTFU Guidelines encompass the following:

Assessment of yield and utility of the LTFU Screening Guidelines—The Guidelines use consensus-based recommendations for risk-based screening of late effects. The yield and utility of prospective screening for late effects is not well-characterized. Members of the Survivorship and Outcomes Committee are examining the yield of the Guideline screening recommendations at their respective institutions. Long-term plans are to validate the findings from these single-institution studies via a multi-center collaboration. Information obtained will contribute to the ongoing refinement of recommendations for screening frequencies and modalities for childhood cancer survivors.

Evaluation of cost-benefit of risk-based screening per the LTFU Guidelines—As with any population-based screening recommendation, the LTFU Guidelines contribute additional costs that have to be evaluated in the context of their efficacy in disease prevention. Investigators from the Committee are currently studying the cost-effectiveness of the recommended screening frequency using echocardiography in childhood cancer survivors at high risk for cardiomyopathy due to anthracycline exposure. Preliminary

findings were presented at the 2012 ASCO meeting, [41] with plans to systematically evaluate the cost-effectiveness of all components of the screening recommendations over the next two years.

International collaboration - standardization of LTFU Guidelines recommendations across international cooperative groups—LTFU screening recommendations have been independently established by the North American COG, the Dutch COG (DCOG), the United Kingdom Children's Cancer and Leukaemia Group (CCLG), and the Scottish Intercollegiate Guidelines Network (SIGN). [6,42–44] The non-integrated approach to screening Guideline development has contributed to inconsistencies in recommendations, duplication of efforts, and inefficiency of resources. Since 2010, representatives from all four Guideline efforts have been working to harmonize recommendations across the cooperative groups, utilizing the Appraisal of Guidelines for Research and Evaluation (AGREE) Collaboration [45] model and established standards for Developing Trustworthy Clinical Practice Guidelines of the Institute of Medicine. [46] Harmonization of screening recommendations have been achieved for females at risk for breast cancer following chest radiation exposure, and efforts are near-completion for cardiomyopathy screening following anthracycline exposure. The current strategy will be utilized to critically evaluate all screening recommendations from each of the cooperative groups, setting the stage for international collaborations to evaluate focused implementation strategies and clinical decision-support tools for healthcare providers caring for at risk cancer survivors.

FUTURE DIRECTIONS: KEY STUDIES TO BE PURSUED

Reproductive Health in Survivors of Childhood Cancer

ALTE11C1: Longitudinal Assessment of Ovarian Reserve in Adolescents with Lymphoma—Female adolescent lymphoma patients may experience acute ovarian failure or may resume cyclic menses after therapy and then experience subsequent infertility, premature menopause and health problems associated with ovarian failure, including cardiovascular disease and osteoporosis. [7,47] There are few prospective data in adolescents treated with contemporary therapeutic regimens on incidence of and risks for acute ovarian failure and depletion of ovarian reserve. [48] Using a prospective, longitudinal design, this study will: 1) assess incidence of acute ovarian failure after contemporary cancer treatment regimens in adolescent lymphoma patients; 2) identify the trajectory of decreased ovarian reserve through the first 12 months following gonadotoxic therapy; 3) assess the contribution of drug metabolizing enzyme polymorphisms to the risk for ovarian failure and depletion of ovarian reserve from baseline to post therapy. This study will provide information that is critical for the study of gonadal protection intervention strategies or the impact of fertility preservation approaches such as oocyte and ovarian tissue cryopreservation.

ALTE12C1- Testicular Effects in Osteosarcoma Survivors Treated with Modern Chemotherapy—Among male adolescent and young adult cancer survivors, one of the most important challenges faced is the toxic effect of cancer therapy on reproductive function, especially spermatogenesis. [7,49] While the toxicity due to alkylators such as cyclophosphamide, chlorambucil, and high-dose busulfan is well-described, [49] less is known regarding the pathogenesis and prevalence of impairments in spermatogenesis associated with cisplatin or ifosfamide, two chemotherapeutic agents frequently used for the treatment of many childhood cancers. Most of our knowledge regarding cisplatin-related impairments in spermatogenesis come from germ cell tumor patients with known gonadal dysfunction at diagnosis who subsequently receive potentially gonadotoxic chemotherapy

and/or radiation and surgery. [50] There is a gap in knowledge regarding the effects on reproductive health of cisplatin in non-germ cell cancer populations and the effects of ifosfamide without cyclophosphamide. Utilizing a cross-sectional study design and drawing upon the advantages offered by prior cooperative group trials, this study will evaluate the prevalence and spectrum of impairments in spermato- and steroidogenesis in survivors of osteosarcoma treated with cisplatin with or without ifosfamide. Information obtained from the current study will lead to improvements in patient counseling and may allow clinicians the opportunity to target fertility preserving technologies male cancer patients at highest risk for infertility.

Cardiovascular Health in Survivors of Childhood Cancer

Health Effects after Anthracycline and Radiation Therapy (HEART): Dexrazoxane and Prevention of Anthracycline-related Cardiomyopathy— Anthracycline-related heart failure is a leading cause of morbidity and mortality in survivors of childhood cancer. [36] Dexrazoxane (DRZ), an ethylenediaminetetraacetic acid (EDTA)-like bisdioxopiperazine that decreases oxygen free radicals via intracellular iron chelation, has been used and tested as a cardioprotectant. [51] However, there is a paucity of information on the long-term efficacy of DRZ for heart failure risk reduction. [51] This study will evaluate cardiac outcomes in long-term survivors of Hodgkin lymphoma and ALL, treated on legacy cooperative group trials that involved randomization to anthracycline +/− DRZ. Event free survival and overall survival was identical in the two arms of all three studies. [52,53] As a result, it is critical to evaluate the cardioprotectant effect of the randomization question. Eligible survivors will be contacted and brought in to various treatment institutions for a comprehensive evaluation of cardiovascular health that includes clinical and sub-clinical measures of cardiac function. This study addresses an important area of concern for children and adolescents undergoing treatment with anthracyclines. In addition, the proposed study will also be one of the first to comprehensively evaluate the long-term efficacy of an intervention for prevention of late effects, years after completion of therapy.

Cardiometabolic Status in Childhood ALL—Adult survivors of childhood ALL have an increased prevalence of obesity and insulin resistance, and may be at risk for developing diabetes, dyslipidemia and metabolic syndrome, all known to be potent risk factors for premature cardiovascular (CV) disease. [54] A recent study demonstrated a high prevalence of cardiometabolic derangement 2–14 years after ALL treatment when compared to matched controls without a history of cancer. [55] Importantly, the investigators found no association between time since diagnosis and the cardiometabolic risk factors, suggesting that the unfavorable profile is likely established early in the course of survivorship. [55] Using a novel study design, these same investigators plan to evaluate the trajectory of cardiometabolic change soon after completion of ALL therapy, setting the stage for a comprehensive assessment of the pathophysiology/mechanistic associations of these adverse cardiometabolic risk factors with cancer and its therapy. This will provide researchers and healthcare providers with important information regarding the timing of cardiometabolic risk screening and intervention. Importantly, this study should establish a cohort of patients with ALL, well characterized early in the course of disease, where the longitudinal trajectory of cardiometabolic risk profile can be assessed in the context of clinically overt cardiovascular disease developing later in life.

CONCLUSION

The growing population of childhood cancer survivors carries a significant burden of morbidity. Future survivorship-focused studies will need to continue ongoing examination

of health-related outcomes, incorporating insight gained from biology studies to develop novel screening and prevention strategies for survivors of childhood cancer. In the cooperative group setting, these efforts will need to be facilitated by established infrastructures to conduct survivorship research such as the services offered by the Long-term Follow-up Center. Information obtained from these studies can then inform standardized evidence-based long-term care to the growing population of survivors, providing timely transfer of health-related information to patients, families, and healthcare providers.

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