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Children's Oncology Group's 2023 Blueprint for Research: Cancer Control and Supportive Care

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Cancer Control and Supportive Care Committee

Abstract

The objective of the Cancer Control and Supportive Care (CCL) committee in the Children's Oncology Group (COG) is to reduce the overall morbidity and mortality of therapy-related toxicities in children, adolescents, and young adults with cancer. We have targeted five major

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domains that cause clinically important toxicity: 1) infections and inflammation; 2) malnutrition and metabolic dysfunction; 3) chemotherapy-induced nausea and vomiting; 4) neuro- and oto-toxicity; and 5) patient-reported outcomes and health-related quality of life. Sub-committees for each domain prioritize randomized controlled trials and biology aims to determine which strategies best mitigate the toxicities. The findings of these trials are impactful, informing clinical practice guidelines (CPGs) and directly leading to changes in the standard of care for oncology practice. With the development of new therapies, there will be new toxicities and the COG CCL committee is dedicated to developing interventions to minimize acute and delayed toxicities, lessen morbidity and mortality, and improve quality of life in pediatric and young adult patients with cancer.

BACKGROUND AND RATIONALE FOR COMMITTEE'S WORK

Many children, adolescents, and young adults (AYA) with cancer undergoing treatment with chemotherapy, radiotherapy, surgery, and cellular therapy have a high risk of developing therapy-related complications. Some toxicities primarily occur while on therapy and either resolve quickly or can persist long-term; other long-term toxicities are not apparent until many years off therapy. Two committees within the Children's Oncology Group (COG) are focused on decreasing the burden of these therapy-related complications. The Cancel Control and Supportive Care Committee (CCL) focuses on assessing toxicities and designing interventions that mitigate complications that occur during cancer-directed therapy and try to both prevent them occurring and limit their short and long-term severity. The Survivorship and Outcomes (LTE) committee focuses primarily on interventions after completion of cancer-directed therapy. The two committees align with the disease committees and key discipline committees such as the Behavioral Sciences, AYA, and Nursing Committees to ensure that there is a coordinated effort to conduct research with a shared aim of decreasing our patients' burden of acute and long-term complications and improving both the quantity and quality of their lives.

As outlined in our 2013 Blueprint, the CCL committee and its respective sub-committees have primarily concentrated their efforts on the following four therapy-related complications: 1) infections and inflammation; 2) malnutrition and metabolic dysfunction; 3) chemotherapy-induced nausea and vomiting (CINV); and 4) neuro- and oto-toxicity.[1] However, the committee recognizes that other therapy-related complications exist that do not neatly fit into these buckets and we enthusiastically address these whenever a promising intervention is proposed for a clinically important supportive care problem. For example, the risk of venous thromboembolism (VTE) following treatment with asparaginase during acute lymphoblastic leukemia (ALL) induction was studied in ACCL1333 and demonstrated that apixaban prophylaxis resulted in lower rates of VTE obese patients without an increase in major bleeding events.[2] The fifth sub-committee of CCL is focused on patient reported outcomes (PROs) and health-related quality of life (HRQoL) and interweaves throughout almost every other committee in COG. This sub-committee identifies key elements of a proposed intervention where capturing the patient's perspective and experiences can give improved perspective if a given intervention should be used. Additionally, the CCL committee has two other important initiatives: CPG endorsement and toxicity-reporting.

CANCER CONTROL AND SUPPORTIVE CARE: AREAS OF FOCUS

Infection and Inflammation

Infections are an important source of morbidity and mortality in children and AYAs with cancer, responsible for over half of treatment-related deaths, with patients receiving chemotherapy for leukemia or lymphoma and those undergoing allogeneic hematopoietic cell transplant (HCT) most vulnerable.[3] Initially, the Infections and Inflammation sub-committee focused on defining the epidemiology of infections across these high-risk populations and revealed bacterial infection and invasive fungal disease (IFD) to be prominent sources of treatment related morbidity and mortality.[1]

These infections can be difficult to diagnose and successfully treat in children with suppressed immune systems. As such, the Infections and Inflammation sub-committee designed a series of randomized trials to determine the efficacy of various prophylactic interventions. ACCL0933 demonstrated that prophylaxis with caspofungin was more effective than fluconazole for pediatric patients with acute myeloid leukemia (AML), while ACCL1131 suggested that caspofungin did not significantly reduce IFD compared to fluconazole or voriconazole prophylaxis in the first 6 weeks after HCT receipt although interpretation was limited as the study was closed early due to a lower than anticipated event rate.[4,5] Regarding prevention of bacterial infections, ACCL0934 demonstrated that levofloxacin prophylaxis significantly reduced the risk of bacteremia among children with relapsed ALL, AML, and those undergoing HCT, while ACCL1034 found that chlorhexidine gluconate bathing did not reduce the risk of central line associated bloodstream infection in children with cancer or allogeneic HCT recipients.[6,7] Collectively, this series of randomized clinical trials informed the development of international CPGs for prevention of bacterial infections and IFD in pediatric patients with cancer.[8,9]

The infrastructure and datasets from these clinical trials have been utilized for prospective biomarker studies and retrospective observational studies, respectively. There have been two fungal biomarker studies completed; one assessed serial galactomannan (GM) and beta-d-glucan (BDG) testing for early detection of IFD in AML patients receiving either caspofungin or fluconazole prophylaxis and a second assessed BDG serial testing in allogeneic-HCT recipients receiving either caspofungin or azole prophylaxis.[10,11] These biomarkers were not effective in identifying IFD, thus informing clinicians to not use these diagnostic tools in routine surveillance for IFD. The dataset from the ACCL0934 levofloxacin prophylaxis study was leveraged to document that musculoskeletal impairments were common among children with leukemia and HCT recipients but not attributable to levofloxacin exposure.[12] These findings were important to better understand the safety profile of levofloxacin prophylaxis.

It is now apparent that children and AYAs continue to have increased risks for infection after completion of therapy.[13] In an ongoing study, the sub-committee is partnering with adult clinical trials groups to assess the immune response to COVID vaccination in patients receiving chemotherapy for cancer (ACCL21C2). This study will provide insights regarding the differential impact of chemotherapy regimens on immune response to vaccination and should provide a platform for future investigations of other vaccines such as influenza or

varicella. The sub-committee is also partnering with the COG LTE committee on a pilot study assessing comprehensive immune recovery in children that have completed ALL therapy. Results will inform a future collaborative proposal for a large revaccination study in this patient population.

Severe oral mucositis remains a significant cause of morbidity in childhood cancer therapy and several studies have attempted to address this complication. The trial ACCL1031 evaluated the use of Caphosol rinses in HCT patients and found it did not reduce mucositis in comparison to placebo.[14] These trials helped to refine current CPGs.[15]

In the future, the ID sub-committee will continue to expand its footprint through development of new concepts. ACCL1932 will activate in 2023 and will assess the efficacy of letermovir prophylaxis in preventing CMV reactivation among high-risk HCT recipients, based on evidence of benefit in the adult population.[16] Two other study concepts under development include ACCL2032, which proposes to assess a novel antifungal agent, rezafungin, to prevent IFD in high-risk ALL patients during induction therapy, and ACCL2331, which plans to assess the benefit of daily xylitol wipes on bacteremia and mucositis in AML patients, based on evidence of benefit in the HCT population.[17]

Malnutrition and Metabolic Dysfunction

Disruption of nutrition and metabolic functions in pediatric and AYA cancer patients lead to acute and long-term sequelae impacting treatment tolerance and adherence, drug distribution and clearance, vulnerability to treatment-related toxicities, HRQoL, and numerous downstream late effects impacting morbidity and mortality of childhood cancer survivors [18,19]. Mounting evidence demonstrates the critical role of nutritional status in the development, progression, metastasis formation, and treatment response of multiple cancers, and this is a potentially modifiable and targetable prognostic factor [18–24].

However, significant gaps in knowledge persist with challenges in identifying age-appropriate, effective interventions that improve outcomes in childhood and AYA cancer. The focus of clinical trials in nutrition and metabolic function through the COG, has therefore included a dual-pronged approach: 1) identifying and closing knowledge gaps in nutritional science; and 2) evaluating efficacy of targeted nutritional interventions in specific populations. Prior studies developed by the Malnutrition and Metabolic Dysfunction subcommittee have focused on upon malnutrition (including both under and over-weight) and use of nutritional supplements or pharmaceuticals to mitigate treatment-related adverse effects. Malnutrition in childhood and AYA cancer patients is common and appetite stimulation leading to increased food intake can prevent cancer-related cachexia [25]. Another recent trial ACCL1633, investigated the effectiveness of Lactobacillus plantarum (LBP) for prevention of acute graft versus host disease (aGVHD) but in early planned interim analysis suggest futility (M. Nieder, verbal communication).

We held a Nutrition State of the Science meeting in October 2018, which convened researchers across the field exploring current knowledge and unanswered key questions in nutritional oncology including topics across gut microbiome [23], under and over-weight/obesity [26,27], body composition [23], hyperglycemia [28], and exercise [29,30]. Results of this

summit were described in a subsequent Journal of the National Cancer Institute Monograph [31–33]. Subsequent work led to the development of ACCL1931 (levocarnitine prophylaxis for asparaginase-associated hepatotoxicity), the first COG-led cross-consortium CCL study and the first AYA-specific CCL trial due to activate in 2023[34], and a new CCL concept evaluating the impact of continuous glucose monitoring on glycemic control in ALL [28].

While causal evidence of the impact of the microbiome on cancer biology is still in its infancy, cancer-modulating interactions and influences on cancer therapy are key scientific questions driving future directions of this subcommittee as the research landscape in nutritional oncology expands [35]. From a systems approach, this committee will promote the development of nutritional concepts through support of pilot work, promotion of funding opportunities to explore preliminary data collection, and expand partnerships to promote collaboration across the National Clinical Trials Network (NCTN). Key interest areas include lipidomics, metabolomics, and the gastrointestinal microbiome with plans to build on recent progress in nutritional genetics.

Chemotherapy-Induced Nausea & Vomiting

Nausea and vomiting due to chemotherapy are clinically important adverse effects of cancer treatment and lead to nutritional deficits and decreased quality of life.[36,37] Since the inception of the CINV sub-committee, CINV control has generally improved through the development and implementation of CPGs on its prevention and treatment.[38–41] The CINV sub-committee seeks to continue to improve CINV control so that more pediatric cancer patients are unaffected by CINV. New antiemetic interventions and new applications of known interventions are evaluated for study.

The CINV sub-committee initially focused on understanding evidence gaps that could be addressed and on developing foundational evidence to support future interventional trials. Examples of past and current multi-center projects are: 1) retrospective evaluations of CINV control in patients receiving gabapentin or dronabinol;[42] 20 feasibility studies of olanzapine and Bright-Ideas training;[43] and 3) nausea severity patient-reported outcome digital application development.

A trial evaluating the contribution of acupressure wrist bands to CINV control was initiated within the COG (ACCL1032) in 2011. It concluded that acupressure bands do not improve CIN control in pediatric patients receiving highly emetogenic chemotherapy.[44] An active industry funded study (ACCL2121) aims to describe the pharmacokinetics and safety of IV aprepitant (Cinvanti®) given as a single dose or a 3-dose regimen to pediatric patients receiving highly or moderately emetogenic chemotherapy. This product offers the potential advantages of peripheral vein administration, low incidence of infusion-related and hypersensitivity reactions and short infusion time. Thus, the findings of this study will benefit patients, families as well as institutions.

Integration of knowledge regarding patient-specific and treatment-related risk factors for CINV is critically needed to ensure that CINV prophylaxis for each pediatric patient is optimized. An algorithm that can be used to individualize the CINV prophylaxis for chemotherapy-naïve patients will be developed and validated. The CINV sub-committee is

developing a study protocol to compare CINV outcomes in pediatric patients who receive individualized, algorithm-based CINV prophylaxis versus the standard of care.

Neuro- and Oto-toxicity

Development of neurologic and otologic toxicities are major long-term morbidities of cancer-directed therapy, often with permanent deficits. A major effort of the group has been to move from post-treatment symptom remediation and prevention of further decline to active neuroprotection during therapy.

Cognitive dysfunction is a devastating sequela of treatment for children with brain tumors and some children with ALL.[45–47] While neurocognitive deficits in children with brain tumors who receive cranial irradiation is well understood, there has been conflicting evidence if cognitive impairment in ALL is due to treatment and/or receipt of repetitive anesthesia.[47] Consequently, the historic strategy in CCL has been to focus on interventions for children with brain tumors and to better understand the natural history of cognitive function in children with ALL and other cancers.

ALTE07C1 was initially a stand-alone study to assess neurocognitive function in survivors of brain tumors (ACNS0331[48] & ACNS0332) and was subsequently embedded in interventions for ependymoma (ACNS0831). The ALTE07C1 battery has since evolved into the ‘COG Neurocognitive Battery,’ which is the standard assessment of cognition using pencil and paper used across COG studies. Cogstate is a computerized cognitive assessment tool with some distinct advantages, including that there is no requirement for a neuropsychologist to administer, it can be administered in the clinic setting, and requires 20-30 minutes to complete, making its use appealing for adaptation across studies and across disease groups. Studies in different disease groups have used both the COG Neurocognitive Battery and Cogstate to assess overall neurocognitive function. In the pediatric high-risk ALL trial AALL1131, there is an embedded longitudinal study of neurocognitive function that provides dysfunction estimates and identifies children at greatest risk for cognitive dysfunction.[49]

Historically, we have addressed neurocognitive difficulties after they appeared either via pharmacological intervention or cognitive remediation. The first interventional trial in COG for remediation of cognitive deficits in children with brain tumors has recently been completed (ACCL0922) comparing modafinil to placebo and using Cogstate to assess cognitive functioning. Data from this study was key to inform effective use of computerized cognitive assessments in further studies to assess cognitive outcomes in subsequent CNS studies (ACNS2031, ACNS1831, ACNS1832, ACNS1833) but did not show that modafinil was an effective intervention (N. Ullrich, personal communication).

There is a critical need for novel and efficacious treatment strategies to mitigate cognitive impact of treatment. A pilot, limited-institution feasibility study using CogMed computerized training immediately following treatment with cranial irradiation (ACCL10P1) has recently completed enrollment and includes assessments using Cogstate and the COG Neurocognitive Battery. In a new study, we are now trying to prevent cognitive late effects from occurring. ACCL2031 is a randomized, placebo-controlled trial

of memantine to prevent cognitive decline after cranial irradiation in children with a brain tumor. Cognitive function as assessed by Cogstate at 12 months following radiation is the primary outcome, with multiple exploratory aims of neuroimaging correlates, biomarker studies and concurrent collection of functioning using the COG Neurocognitive Battery.

Ototoxicity is another important treatment-related adverse event. Cisplatin is the treatment backbone for many newly diagnosed non-hematologic tumors in children and AYAs, including neuroblastoma, hepatoblastoma, medulloblastoma, osteosarcoma, and malignant germ cell tumors.[50] While cisplatin is effective, it also damages the cochlea, leading to progressive and permanent hearing loss in most children who receive platinum-intensive therapy.[51] Hearing loss, in turn, leads to cognitive deficits, difficulties with socialization, and reduced academic and work functioning.[52] Sodium thiosulfate (STS) was evaluated for otoprotection in ACCL0431, with a nearly 50% reduction in the incidence of hearing loss among children who received STS, though with lower EFS in those with metastatic disease.[53,54] ACNS2031 recently launched to assess otoprotection in children with low-risk medulloblastoma. STS (Pedmark®) has recently been granted approval by the Food and Drug Administration for otoprotection in children with localized disease receiving platinum-intensive chemotherapy. A CPG provides guidance for medical interventions for the prevention of cisplatin-induced ototoxicity in children and AYAs.[55]

A survey of CCL responsible investigators suggests that institutions are supportive of continued research into pediatric otoprotection that includes assessment of tumor response and survival.[56] In the future, the neuro- and oto-toxicity sub-committee is planning to study earlier interventions to prevent neurocognitive decline in patients with ALL. Furthermore, new otoprotection trials are warranted to expand the use of STS, determine safety and anti-tumor activity in different tumor types and with metastatic disease, and to assess new modes of administration. Pilot studies using depot and trans-tympanic administration of STS and concomitant systemic use of STS with other otoprotectants are underway.

Patient Reported Outcomes and Quality of Life

Capturing PROs from children with cancer and their caregivers is essential for designing future trials / interventions focused on minimizing non-infectious treatment toxicities and optimizing patient/family functioning. Studying the impact of therapies on activities of childhood development is dependent on PROs, as many of these domains are not readily observable to clinicians. Historically there has been a paucity of data examining HRQoL and PROs throughout therapy and into survivorship in pediatric and AYA trials.

Over the past decade, several COG disease-specific trials have embedded HRQoL aims. AALL0932 for standard-risk ALL patients found that a substantial proportion of patients reported physical and/or emotional functioning impairment early in therapy which persisted.[57] AAML1031 collected patient and caregiver proxy measures to describe HRQoL across chemotherapy cycle for AML, finding that the extent and prominence of fatigue was a major symptom.[58] Currently, AALL1731 for standard risk ALL is examining the impact of therapy, including the incorporation of blinatumomab, on caregiver burden and investigating parent- and patient-reported symptoms longitudinally through intensive

therapy. Such studies have helped identify critical timepoints to intervene or symptoms to target, providing opportunities to attempt to improve HRQoL and functioning of patients.

In AALL1731, as well as the Hodgkin Lymphoma trials AHOD1331[59] and S1826, the experimental arm of the parent trial includes immunotherapy, while in AGCT1531 two platinum agents for treatment of germ cell tumors are compared. Embedding longitudinal HRQoL/PRO aims in these types of trials is of great importance because impact on HRQoL or symptom burden may be the deciding factor for which regimen to recommend if there is no difference in treatment efficacy and can suggest interventions to manage expected symptoms and/or impact on functioning from the superior regimen, as well as providing anticipatory guidance to families. There are additional PRO concepts in development in osteosarcoma, neuroblastoma, and leukemia trials that will provide similar information.

There remain several challenges for PRO research, such as early integration of PROs into trial design, efficient data collection, and minimizing site burden. These challenges have begun to be addressed through the successes of the Childhood Cancer Data Initiative funded NCTN AYA-PRO task force (please see AYA Committee Blueprint) which developed through expert consensus a battery of recommended, validated PRO measures that can be adapted for use across AYA trials, provided education on statistical analysis of PRO data, and is now piloting electronic data capture being centrally managed at COG in five current / upcoming COG trials.[60] Building on these successes and the recognition of the cross-discipline nature of PRO research, a working group of physicians, nurses, and behavioral scientists has formed with the overarching goal of increasing capacity in COG to incorporate meaningful PROs aims into pediatric oncology research. Through the efforts of this working group, processes for PRO incorporation into clinical trials across diseases will be streamlined in COG, PRO expertise in COG will be enhanced, and data will ideally be more efficiently collected and analyzed, with the goal of improving the lives of pediatric cancer patients.

Standardizing Supportive Care: The Supportive Care Guidelines Working Group

The COG recognizes that standardized delivery of evidence-based supportive care across the more than 220 COG institutions in North America and beyond minimizes disparities, enhances trial conclusions, and improves patient outcomes.[61,62] Therefore, we identify and use a standardized process to evaluate for endorsement rigorously developed, evidence-based, supportive care CPGs and widely disseminate these to COG clinicians and families for recommended local implementation via the COG Supportive Care Guideline website (https://childrensoncologygroup.org/cog-supportive-care-endorsed-guidelines).

Improving Toxicity Reporting: The Toxicity Task Force

The COG has demonstrated that the current adverse event (AE) reporting in COG trials is inconsistent and under-reported.[63–65] After surveying COG institutions, we identified and have developed strategies to improve and standardize AE reporting in three main areas. These included creating a guidance document on how to write the AE section of new protocols, increasing training modules on AE reporting, and providing guidance for clinical research associates on interpreting AE definitions.[66] Having a complete understanding of the

therapy-related complications experienced by our patients, will allow us to design effective interventions that prevent (ideally) or treat (if needed) such toxicities.

SUMMARY AND CHALLENGES

Treatment-related toxicities are common during receipt of chemotherapy, radiotherapy, and cellular therapy in children and AYAs with cancer. These toxicities can result in significant morbidity and decreased quality of life and even be life-threatening. Accurate measurement and reporting of these toxicities is critical to understanding the scope of the problem. High-quality, large, multicenter trials are needed to determine if certain approaches can successfully mitigate the risk, and the COG is one of the only consortiums capable of successful performing them. Designing and implementing these trials can be challenging due to various factors, including: 1) a paucity of plausible agents that address the pathophysiology of certain complications; 2) limited funding for completing pilot trials that generate preliminary safety and efficacy data to justify larger, definitive phase three trials; and 3) competition with cancer-directed trials for patient/family and institutional bandwidth for clinical trial consenting and management. Finally, those interventions that do decrease treatment-related toxicities then need to be integrated into CPGs to be broadly implemented at the local treatment sites.

Despite these challenges, successful interventions have been identified by the CCL Committee and other similar groups around the world, all of which directly contribute to improved outcomes and quality of life in children, adolescent, and young adults with cancer. The CCL committee will continue to develop trials that inform best practices for prevention of toxicities and improvement in quality of life for children, adolescents, and young adults with cancer.

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Abbreviations key

CCL	Cancer Control and Supportive Care
COG	Children’s Oncology Group
CPG	clinical practice guidelines

AYA	adolescents, and young adults
LTE	Survivorship and Outcomes
CINV	chemotherapy-induced nausea and vomiting
VTE	venous thromboembolism
ALL	acute lymphoblastic leukemia
PRO	patient reported outcomes
HRQol	health-related quality of life
HCT	hematopoietic cell transplant
IFD	invasive fungal disease
AML	acute myeloid leukemia
GM	galactomannan
BDG	beta-d-glucan
LBP	Lactobacillus plantarum
aGVHD	acute graft versus host disease
STS	Sodium thiosulfate
NCTN	National Clinical Trials Network
AE	adverse event

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