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Children's Oncology Group's 2012 Blueprint for Research: Cancer Control and Supportive Care

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Abstract

In cancer control research, the objective is to reduce overall morbidity and mortality by decreasing acute and delayed treatment-related toxicities in all children with cancer. To date, the Children's Oncology Group (COG) has focused on infection, neurocognition, quality of life (QoL), and nutrition/antiemetics. COG is conducting randomized controlled trials (RCTs) to determine prophylaxis strategies that will reduce infections in high-risk populations. Two RCTs are determining if modafinil or computerized cognitive training improve cognitive functioning in pediatric brain tumor patients. QoL is being assessed in acute leukemia patients. Improved supportive care outcomes will only occur when the most effective interventions are established.

Keywords

cancer control; cognition; infection; supportive care

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INTRODUCTION

Background and Rationale

Cancer control and supportive care (CCL) research focuses on reduction of acute and delayed treatment-related toxicities in children with cancer. Progress has resulted from the work of many investigators from around the world. The following article is designed to illustrate some of the major issues facing children with cancer and how the Children's Oncology Group (COG) has focused its efforts in improving symptom control. COG CCL has focused on addressing the most important clinical issues that affect children receiving treatment for cancer. The broad areas deemed important by healthcare providers and by parents are toxicities that impair quality of life (QoL) and those that result in mortality. Based on these characteristics, COG selected the following areas for research: (i) infection and inflammation, including prevention of bacterial and fungal infections and treatment of mucositis; (ii) neurological complications, including peripheral neuropathy, hearing loss and cognition; (iii) palliative care and symptom control; and (iv) nutrition and antiemetic control. CCL research has also focused on developing or validating instruments relevant to symptoms control.

Historically, accrual to CCL studies has been poor. Consequently, much attention has focused on developing questions considered most important by clinicians, obtaining extra-mural funding for investigations and developing strategies to enhance accrual such as close communication with centers and provision of aids to identify eligible patients.

Infection and Inflammation

Infections are one of the most common causes of morbidity and mortality in children receiving intensive chemotherapy such as those with acute myeloid leukemia (AML), relapsed acute lymphoblastic leukemia (ALL) and recipients of autologous or allogeneic hematopoietic stem cell transplantation (HSCT).[1–4] Investigators working with COG have completed a series of studies that described the major infectious issues in intensively treated children, which led to the development of key prophylaxis trials in COG. Data used to inform these analyses were derived from COG and legacy Children's Cancer Group (CCG) AML therapeutic trials and demonstrated specific infection types that were prevalent and contributed to mortality. Using these analyses, the cumulative incidence of an invasive fungal infection was 14.3 ± 3% on the most recently completed COG AML clinical trial (AAML0531) [5]. Invasive fungal infections were identified as the most common contributor to infectious mortality in pediatric AML, with both *Aspergillus* species and *Candida* spp. contributing similarly [3,4,6]. Furthermore, invasive bacterial infections continue to be prevalent; the cumulative incidence on AAML0531 was 82 ± 4% [5]. These findings highlight that in spite of the best available current supportive care, invasive bacterial and fungal infections continue to be problematic in children receiving treatment for AML. These observations led to the development of four infection prophylaxis randomized controlled trials (ACCL0933, ACCL1131, ACCL0934, and ACCL1034). These trials are studying the efficacy of caspofungin to reduce invasive fungal infection (ACCL0933 and ACCL1131), levofloxacin to reduce bacteremia (ACCL0934) and chlorhexidine gluconate

(CHG) cleansing to reduce central line associated bloodstream infection (CLABSI, ACCL1034).

Another infection-related issue relevant to children with cancer is the utility of prophylactic and therapeutic growth factors. While there are a large amount of data to guide prophylactic granulocyte colony-stimulating factor (G-CSF) use [7], there are far fewer data on whether therapeutic G-CSF at onset of fever and neutropenia (FN) is beneficial. In AS973, children who did not receive prophylactic G-CSF were randomized to receive therapeutic G-CSF at 5 mcg/kg/day or no G-CSF within 24 hours of antibiotics for FN. Among 66 children, G-CSF significantly reduced the duration of neutropenia and FN recovery time. However, there was no significant difference in time to resolution of fever. Hospitalization was significantly reduced by 1 day [8].

Oral mucositis is another common consequence of chemotherapy. It is important because it is painful and reduces QoL. In addition to pain, morbidity of mucositis includes the inability to eat and drink. These symptoms may be sufficiently severe to result in hospitalization for pain control, hydration, and alimentation. Furthermore, oral mucositis is associated with ulceration, which provides a portal of entry for oral microflora and may lead to bacteremia and sepsis. Finally, oral mucositis has become a major dose-limiting toxicity and consequently, may limit delivery of anti-cancer therapy [9]. It is one of the most distressing and prevalent side effects of chemotherapy and HSCT [10]. There are currently no feasible interventions that can reduce mucositis in children with cancer.

Traumeel S, a homeopathic remedy, was evaluated as a preventative strategy for oral mucositis in COG (ACCL0331). This study randomized 195 patients receiving autologous or allogeneic HSCT to topical Traumeel S or placebo. This trial determined that Traumeel S was not effective at preventing or treating oral mucositis [11].

COG is currently studying topical caphosol as a preventative strategy in HSCT. Within this study (ACCL1031), intensive mucositis evaluation training to site staff has been successfully implemented through webinars or in-person training sessions.

Neurological Complications

Cognitive dysfunction is one of the most devastating sequelae of treatment for children with brain tumors and some children with ALL. While neurocognitive deficits in children with brain tumors who receive cranial irradiation is well understood [12], there has been conflicting evidence about whether children with ALL experience cognitive impairment as a consequence of treatment. In ACCL0131, neuropsychological outcome was measured for children enrolled on POG9605 and POG9201, two ALL therapeutic trials. Among the 66 children enrolled, the average intelligence quotient (IQ) was less than 85. However, COG also examined neurocognitive outcomes for children enrolled on CCG105. In these children with “intermediate risk” ALL, among the 106 children randomized to not receive whole brain cranial irradiation, IQ increased slightly over a 48-month window, always remaining close to measured normative values (personal communication, R Annett, September 2012). Of note, even children who received 1,800 cGy of whole brain irradiation only demonstrated

modest declines in IQ over 4 years (less than five points). Other research conducted in CCG illustrated that IQ for children with standard risk ALL approached normative values [13,14].

Other pediatric cancer groups have also contributed to this area substantially. Studies conducted by St. Jude Children's Research Hospital highlighted that children with ALL may have more difficulties with attention rather than intellectual functioning, academic skills or memory. Studies conducted by St. Jude and by the Dana Farber ALL Consortium demonstrated that children receiving more intensive chemotherapy may be at higher risk of neurocognitive deficits [15,16]. These findings justify a focus on children with high-risk ALL.

Consequently, the current strategy in CCL has been to focus interventional trials on children with brain tumors and to better understand the natural history of cognitive function in children with high-risk ALL. More specifically, the interventional trials for children with brain tumors include modafinil (ACCL0922) and computerized cognitive training (ACCL10P1). COG has embedded a longitudinal observational study of neurocognitive function in the high-risk ALL clinical trial (AALL1131, neurocognitive ancillary aim).

Palliative Care and Symptom Control

There is a paucity of information about QoL in children receiving treatment for cancer whereas more is known about QoL in long-term survivors [17]. Children receiving intensive chemotherapy have worse QoL [18]. However, there is currently a lack of data that defines QoL in a longitudinal fashion for children with cancer. Better definition of QoL for cohorts of children treated similarly will help define the extent (or absence) of the problem and will also identify the types and timing of interventions which would be most beneficial. QoL was assessed in children enrolled on AALL0331 for standard risk ALL. At 1 month after diagnosis, 33% of 175 children experienced social withdrawal and adaptive concerns. In addition, 39% of children demonstrated at-risk or clinical internalizing problems comprised of anxiety, depression, and somatization [19].

COG also measured QoL longitudinally in children with osteosarcoma. In children enrolled on AOST0331, at the first time point which was prior to local control (surgery), females under the age of 16 years demonstrated worse QoL and all patients over the age of 16 years rated school functioning and social functioning as the worst dimensions of health [20–23].

Evaluating QoL in children likely to be cured is important and consequently, CCL is currently evaluating QoL for children with standard risk ALL. However, evaluating QoL in children receiving intensive chemotherapy is also important since QoL is likely to be most impaired in this group. Thus, COG is evaluating QoL in children with AML who receive HSCT and chemotherapy as consolidation strategies. Palliative care has been a much more difficult area to study. A study of COG institutions did note that pediatric palliative care is only offered in 58% of COG institutions [24].

Nutrition and Control of Nausea and Vomiting Due to Antineoplastic Therapy

Nutrition and chemotherapy-induced nausea and vomiting (CINV) are both important to children with cancer. Children and adolescents with cancer who are either over-nourished or

under-nourished experience poorer outcomes and increased toxicities. In one of the largest studies exploring the effect of nutritional status, the relationship between body mass index percentile at diagnosis and survival was collected in 768 children with AML enrolled on CCG2961 [25]. Underweight patients were less likely to survive and were more likely to experience treatment-related mortality compared to middleweight children. Similarly, overweight patients were less likely to survive and had increased treatment-related mortality. In patients treated on CCG1961 for high risk ALL, being at either weight extreme was associated with an increased risk of treatment-related severe non-hematological toxicity, and reduced event free survival and overall survival [26]. Children with intermediate risk rhabdomyosarcoma who were malnourished and treated on COGD9803 experienced increased toxicity (personal communication, M. Burke, October 2012). Taken together, these studies lend support to the importance of preventing the development of malnutrition in children with cancer and examining ways to reduce adverse outcomes associated with overweight status.

The efficacy of cyproheptadine hydrochloride (periactin) was studied within COG (ACCL0423). This sequential Phase 2 study of pediatric oncology patients with a history of disease and/or therapy-related weight loss treated patients with 4 weeks of periactin; those who lost weight after 4 weeks were switched to megace. Seventy patients were enrolled. Fifty of 66 evaluable periactin treated patients (76%) demonstrated a response (average weight gain 2.6 kg and mean weight-for-age *z*-score change of 0.35, $P = 0.001$). Five of the non-responders treated with megace responded (average weight gain of 2.5 kg). The most commonly reported side effect of periactin was drowsiness. One patient on megace developed low cortisol levels and hyperlipidemia. Thus, this study demonstrated that periactin is a safe and effective therapy to promote significant weight gain in children with cancer/treatment-related cachexia [27].

Poor antiemetic control can also exacerbate nutritional challenges and worsen QoL. Nausea and vomiting are among the most severe and bothersome acute toxicities experienced by children receiving chemotherapy according to their parents [28]. Factors which increase the risk of CINV in children have not been identified. For example, the emetic risk of certain chemotherapeutic agents in children is almost entirely based on the experience of adults with cancer [29]. Furthermore, a recent systematic review indicated that only half of children receiving highly emetogenic chemotherapy have complete control of CINV when given standard antiemetic prophylaxis (ondansetron/granisetron plus dexamethasone) [30]. Clearly, our understanding of CINV in children and interventions available to us to prevent it are sub-optimal.

STRATEGIC APPROACH

Reducing morbidity/mortality from infections: based upon data from therapeutic COG trials, both the patients at highest risk of infection outcomes and the nature of those specific infections were identified. There are four Phase 3 clinical trials within COG designed to prevent invasive infections in high-risk children (ACCL0933, ACCL1131, ACCL0934, and ACCL1034).

CCL has developed two clinical trials focused on antifungal prophylaxis. The standard of care for many years has been fluconazole prophylaxis for children at higher risk of invasive fungal infection. However, fluconazole only has coverage against some yeasts and no activity against molds. While prophylaxis with broad-spectrum antifungals such as caspofungin is attractive, it is unknown whether this strategy is better than empiric therapy in which broad-spectrum antifungal agents are initiated with persistent fever [31]. ACCL0933 is randomizing children with AML to prophylaxis with either fluconazole or caspofungin during periods of neutropenia. ACCL1131 is also evaluating caspofungin but is randomizing children undergoing allogeneic HSCT to caspofungin versus fluconazole or voriconazole, with each institution choosing the comparator arm. Both ACCL0933 and ACCL1131 will explore whether host genotype influences the rate of invasive fungal infection in pediatric cancer.

Given that invasive bacterial infection is also highly prevalent and results in morbidity and mortality, COG is also conducting trials specifically aimed at this infection type. In choosing antibiotic prophylaxis strategies in high-risk populations, it was important to consider viridans group streptococcal [32] and pseudomonal coverage. ACCL0934 is randomizing children with relapsed ALL, AML, and autologous or allogeneic HSCT recipients to either levofloxacin prophylaxis or usual care for two cycles of chemotherapy or one transplant procedure. An important ancillary aim associated with this study is the evaluation of resistance in organisms colonizing the gastrointestinal tract. This description of the effect of antibacterial prophylaxis on resistant organisms will be a unique contribution to the literature and will help determine whether on balance, prophylaxis is a beneficial strategy. ACCL1034 is another randomized prophylaxis study which will determine if daily CHG cleansing can reduce CLABSIs in children with external tunneled central venous catheters. A secondary objective will be to determine whether CHG cleansing decreases acquisition of multi-drug resistant organisms (such as vancomycin resistant enterococci and methicillin resistant *Staphylococcus aureus*) in children with cancer.

These trials should complete accrual over the next 3–4 years. Consequently, the strategy has shifted to focus on developing studies to reduce specific clinically important infections such as *Clostridium difficile* colitis. One agent of particular interest is fidoxamycin, as this agent may be effective in reducing recurrence and does not influence the gastrointestinal microflora.

In terms of mucositis prevention, ACCL1031 is determining whether topical caphosol, a supersaturated calcium and phosphate solution widely used in many HSCT centers, reduces oral mucositis in children undergoing HSCT. The measurement of mucositis is problematic in children with cancer and ACCL1031 will also serve to validate a pediatric specific measure of mucositis termed the Children's International Mucositis Evaluation Scale [33,34]. Future efforts in mucositis prevention will continue to target the highest risk children such as children undergoing HSCT. A potentially interesting intervention to evaluate is low level laser therapy for the prevention and treatment of oral mucositis.

Improving neurocognition in pediatric cancer: our goal is to identify effective interventions to improve neurocognition among children with brain tumors. Currently, the interventions

being evaluated include modafinil (ACCL0922) and computerized cognitive training (ACCL10P1).

ACCL0922 is a COG trial that will target a pharmaceutical intervention, modafinil, at improving neurocognitive function for children who have received therapy for a primary brain tumor. This study is randomizing children who have documented cognitive impairment to either modafinil or placebo for 6 weeks. ACCL10P1 is a study of cognitive training. This pilot study will determine if CogMed, a computerized cognitive training program, is feasible within the co-operative group setting. If feasible, an efficacy study will be developed. Both studies are using a common platform for neurocognitive evaluation, an important consideration for COG trials.

COG is also evaluating neurocognitive function in children enrolled on AALL1131 in a longitudinal fashion. This study will describe the prevalence of cognitive deficits in working memory, executive function, visual motor, processing speed and visual attention in children 6–11 years of age receiving treatment for high risk ALL. This study uses CogState to assess cognitive outcomes (which is also being used in ACCL0922 and ACCL10P1). This study should document the natural history of cognitive changes in children with ALL receiving contemporary therapy.

Improving symptom control in good- and poor-risk groups of pediatric cancer patients: the COG strategy will continue to identify children at the highest risk of poor QoL but more importantly, begin to explore interventions that can improve QoL for both children who can and cannot be cured.

There are currently two embedded trials which will describe the effects of therapy on QoL for children with standard risk ALL (AALL0932) and children with AML (AAML1031). The data in AML are particularly important as they may inform decision making related to HSCT, especially for children with poor risk AML.

Fatigue is a particularly important QoL consideration in children with cancer and there is an intimate relationship between fatigue and sleep disturbance [35]. COG is developing a study of Ramelteon to determine whether this agent can improve sleep in both inpatients and outpatients with cancer.

Improving nutritional status and CINV control: research efforts should focus on designing nutrition interventions for underweight status. Studies to reduce overweight status are less likely to be feasible within the co-operative group setting since they will require a multi-modality approach. The approach to CINV control will be to evaluate novel antiemetic interventions which have demonstrated efficacy in adults.

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