

REVIEW

Children's Oncology Group's 2013 Blueprint for Research: Adolescent and Young Adult Oncology

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on behalf of the COG Adolescent and Young Adult Oncology Discipline Committee

The discipline of Adolescent and Young Adult (AYA) Oncology addresses compelling medical and psychosocial needs of AYA patients across the spectrum of cancer survivorship. To be successful, extraordinary collaboration involving multiple scientific disciplines and specialties is required. While AYA Oncology is international in scope, recent AYA-focused studies conducted in the Children's Oncology Group (COG) have documented survival

disparities, toxicity differences, and biological insights that provide the basis for new COG trials and initiatives for this population. This experience will be useful in leveraging the new United States National Cancer Institute Clinical Trials Network to transform AYA Oncology research. *Pediatr Blood Cancer*

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INTRODUCTION

During the past decade, considerable progress has been made in the relatively new field of AYA Oncology, with multiple investigators identifying a slower rate of improvement in survival compared with younger and older age groups, outlining challenges in caring for this unique population, and beginning to address important scientific questions necessary for improving treatment and support for these patients [1,2]. Yet, much remains to be understood regarding how outcomes disparities and quality of life are affected by factors that include differences in cancer and host biology, tolerance of treatment, adherence to therapy, psychosocial adjustment, and medical decision-making. Relatively poor accrual of AYA patients to United States National Cancer Institute (NCI)-funded clinical trials remains a major problem, coupled with even poorer accession of biospecimens essential for basic research [3]. Finally, unique issues of cancer survivorship have emerged for young adult survivors of childhood cancer, including the need for health care transition for longitudinal follow-up [4]. AYA Oncology is unique as a discipline, in that age rather than a specific disease defines its specialty. Indeed, one of the greatest challenges encountered within this discipline is its reliance on the scientific expertise of clinical and basic investigators working in disparate cancer types and fields such as pharmacology, behavioral sciences, survivorship, and cancer control. To be successful, it is clear that the discipline of AYA Oncology must engage effectively with diverse investigators around compelling questions. As this discipline has become the subject of significant clinical and research interest around the world [5], the focus of this paper is on the recent accomplishments and future directions of AYA Oncology research.

RECENT ADVANCES

As an essential starting point for laying the groundwork for prospective clinical trials addressing distinctively AYA questions, secondary analyses of data sets from relatively large, completed clinical trials represent a rich resource for studies focused on age-related outcomes not among the original study aims. Though retrospective, such observations provide crucial insights leading to efforts to improve outcomes in this age group. This is exemplified by the recent discovery that AYA patients with acute

lymphoblastic leukemia (ALL) have superior outcomes when treated using contemporary pediatric rather than traditional adult therapeutic regimens, a finding now confirmed in multiple international reports [6]. Only multicenter cooperative group trials are likely to offer sample sizes large enough to provide sufficient power for these types of analyses. Utilizing this strategy, existing data sets from COG or legacy group (i.e., Children's Cancer Group, Pediatric Oncology Group, Intergroup Rhabdomyosarcoma Study Group, and National Wilms Tumor Study) studies have been mined to yield the following insights.

Age-Related Differences in Survival

Recently, an Australian registry-based study reported significantly poorer survival over the period 1982–2002 for AYA compared with younger patients with ALL, rhabdomyosarcoma, osteosarcoma, Ewing sarcoma, and Hodgkin lymphoma [7]. Several recent North American studies confirm this trend. In a study of 1,054 evaluable patients treated for high-grade osteosarcoma of any site enrolled on the North American cooperative group trials CCG-7943, POG-9754, INT-0133, and AOST0121, age ≥ 18 years was associated with statistically poorer EFS and OS, adjusting for the presence of metastatic disease and primary site. The 10-year EFS and OS for patients <10 , 10 – 17 , and ≥ 18 years were 55.0%, 55.1%, 36.9% ($P = 0.019$), and 67.9%, 59.7%, 40.8% ($P = 0.043$), respectively [8]. In a study of 1,244 patients treated for Ewing sarcoma on INT-0091, INT-0194, and AEW0031, results indicate that for patients with non-metastatic disease, the hazard ratio for relapse among patients ≥ 18 years old compared with <10 years old is 2.97 (95% CI 1.93–4.56), after adjusting for

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primary tumor site, chemotherapy regimen, and treatment intensity received [9]. In other cancers, however, older patients appear to do as well or better. A recently completed survival analysis for patients with Hodgkin lymphoma treated on POG-9425 and 9426 showed no difference in EFS for patients 15–21 years old versus younger [10]. For newly-diagnosed acute myeloid leukemia (AML), in a retrospective comparative meta-analysis of 517 AYA patients 16–21 years of age treated on either COG studies or Cancer and Leukemia Group B (CALGB) and Southwest Oncology Group (SWOG) studies from 1986 to 2008, 10-year EFS and OS of the COG cohort were superior to the combined adult cohorts ($38 \pm 6\%$ vs. $23 \pm 6\%$, log-rank $P = 0.006$ and $45 \pm 6\%$ vs. $34 \pm 7\%$, $P = 0.026$, respectively) [11]. In a comparison of outcomes (EFS/OS and toxicity) for patients 16–21 years of age versus younger treated on a series of COG trials for newly-diagnosed AML (CCG-2891, -2941, -2961 and AAML03P1), results indicate that OS was only marginally worse for the AYA versus younger patients ($49.7 \pm 7\%$ vs. $54 \pm 3\%$, $P = 0.058$) [12]. Relapse was significantly lower among the AYA group ($30 \pm 7\%$ vs. $41 \pm 3\%$; $P = 0.002$), but this was offset by higher treatment-related mortality (TRM) in the older group.

Age-Related Differences in Treatment-Related Toxicity

In both of the secondary analyses of AML mentioned above, significantly higher TRM was noted for patients 16–21 years old when compared within COG trials to younger patients ($25 \pm 6\%$ vs. $12 \pm 2\%$, $P < 0.001$) [12] or to their peers treated on adult cooperative group trials ($26 \pm 6\%$ vs. $12 \pm 6\%$, $P < 0.001$) [11]. Two other secondary analyses have identified significantly greater incidence of peripheral neuropathy in adolescent vs. younger patients, one in rhabdomyosarcoma (IRS-IV) [13] and another in a combined cohort of Wilms tumor and rhabdomyosarcoma patients [14]. On the other hand, the IRS-IV analysis found significantly less severe cytopenias among older patients [13]. Among patients treated for NCI high risk ALL on AALL0232, fewer AYA patients (≥ 16 years of age) achieved complete remission according to protocol criteria at the end of Induction (59% vs. 74% , $P < 0.0001$) [15]. On this same trial, a significantly higher 5-year cumulative incidence of death in remission was seen for AYA than for younger patients ($4.4 \pm 1.1\%$ vs. $1.8 \pm 0.4\%$, $P = 0.0015$), mostly attributable to infections. Additional differences in treatment-related toxicity, including oral mucositis, peripheral neuropathy, hyperglycemia, and hyperbilirubinemia were also described in these reports [16,17].

Collectively, the above studies paint a picture of clear, if somewhat variable, differences in outcome for AYA patients manifesting in both survival/disease response and tolerance of treatment. No other cooperative groups have undertaken similar analyses, but within COG these have already led to expanded efforts to characterize these differences in greater scope and detail, in some cases by embedding AYA-focused objectives within clinical trials. It is important to acknowledge the many limitations imposed by retrospective analyses, chiefly restrictions on what data elements are available and sometimes their non-comparability across trials. Ultimately, prospective studies building on these observations will permit collection of more complete and useful data, and possibly provide a means for improving the historically poor participation of AYA patients in clinical oncology trials.

Long-Term Follow-Up Services for AYA Survivors of Pediatric Cancer

In a survey of COG institutions ($n = 220$) conducted by the COG Nursing, AYA, and Late Effects (now Survivorship and Outcomes) Committees, nearly half of respondents ($70/161$, 44%) reported having no mechanism for transition of care for adult survivors from pediatric to adult-focused providers and facilities; multiple perceived barriers to this process were captured [18]. This study highlights an area needing increased emphasis, resources and further research to achieve recommended standards for longitudinal, risk-adapted late effects surveillance and comprehensive support for childhood cancer survivors across the lifespan [4].

STRATEGIC APPROACH

AYA Oncology is an emerging discipline. While major obstacles in AYA Oncology have been articulated well, such as slower rates of improvement in survival, outcomes disparities, and poor accrual to clinical trials, there remains a need for more complete characterization of these issues, as well as research into fundamental causes. In addition, systems needed for conducting research effectively in this patient population are, in some cases, under-developed. Therefore, an approach is needed that will move the discipline forward on both fronts. First, the vast resource of existing data sets can continue to be mined effectively and efficiently to provide a wealth of fundamental observations that more fully characterize the differences between AYA and younger patients and generate hypotheses for further exploration through clinical trials and studies of cancer and host biology. However, it is essential that the data be used immediately to develop specific aims that can be incorporated into prospective studies, which permit the collection of more complete and relevant data, as well as evaluation of therapeutic interventions. Based on preliminary observations documenting age-related differences in survival and toxicity [7–17], suspected differences in tumor biology affecting survival and developmental pharmacology influencing treatment tolerance will require AYA-focused studies of cancer and host biology. Second, an opportunity exists for establishing critically important collaborations between pediatric and adult cooperative oncology groups. AYA Oncology is noteworthy in relying on scientific and clinical expertise of both pediatric and medical oncologists. As discussed further below, in the United States the new NCI Clinical Trials Network may provide an ideal opportunity for COG and the four adult cooperative groups to develop partnerships around priority diseases. Building on the successful example of collaboration between COG and CALGB in developing C10403 and AALL0232/AALL1131, similar opportunities exist in areas such as bone and soft tissue sarcomas, AML, Hodgkin lymphoma, certain non-Hodgkin lymphomas, germ cell tumors, thyroid cancer, and melanoma. Efforts will be focused not only on study development, but also maximizing AYA accrual across participating groups.

KEY TRIALS-INITIATIVES TO BE PURSUED

Treatment of Malignancies Characteristic of the AYA Population

In addition to on-going trials in more common diseases such as leukemia and bone sarcomas, several new COG studies are in

development focusing on malignancies that are infrequent overall but concentrated in the AYA population. These include the following: (1) ARTS1221 for non-rhabdomyosarcomatous soft tissue sarcoma (NRSTS), a response-based trial evaluating the efficacy of the tyrosine kinase inhibitor, pazopanib; (2) the Malignant Germ Cell Tumor International Collaboration (MAGIC), undertaken with the United Kingdom Children's Cancer and Leukaemia Group (CCLG), a risk-based trial to reduce use of dose-intensive cisplatin and its toxicity; and (3) a study to determine the feasibility of administering EBV-specific cytotoxic T-lymphocytes after treatment with chemotherapy and radiotherapy to patients with newly diagnosed nasopharyngeal carcinoma.

AYA Cancer Treatment Toxicity Initiative

Excessive chemotherapy-induced toxicity has been documented among adolescents as compared with younger patients [11–14,16,17]. In order to optimize both treatment efficacy and tolerability for AYA patients, this problem must be better characterized and mechanistic hypotheses developed. A logical next step to be pursued within COG is ascertaining common themes of toxicity across diseases and studies, focusing the analysis on candidate toxicities with high frequency and/or high clinical impact among AYA patients using data sets from clinical trials that incorporated common causative agents. These findings are expected to guide development of clinically relevant developmental pharmacology studies involving key chemotherapeutic agents. This will complement such findings as significant gender-specific differences in toxicity and response rates among young adults with select AYA cancers [7]. Similar studies in the context of other treatment approaches used world-wide are needed.

Planned Secondary Analyses

Two new AYA-focused secondary analyses have recently been initiated. The first is *Survival Outcomes and Toxicities between AYA and Younger Patients Treated for Hodgkin Lymphoma on CCG-5942*, which will allow the impact of radiation therapy to be assessed as given in randomized fashion on a backbone of COPP-ABV. This will be followed by a similar analysis of a more contemporary chemotherapy backbone in the recently closed study of intermediate-risk disease, AHOD0331. The other is *Treatment-Related Toxicity and Survival as a Function of Age in Children and Adolescents with Medulloblastoma*, using CCG-A9961 and CCG-99701 datasets, which will allow differences in presentation, survival, and adverse effects of vincristine, cisplatin, surgery, and irradiation to be explored.

Collaboration With Medical Oncology

Historically, one of the major North American barriers to studying AYA cancers has been the lack of any overarching relationship in this arena between the COG and the NCI-funded adult cooperative groups. At the same time, it is clear that most high priority cancers in the AYA age group of 15–39 years span the fields of both pediatric and medical oncology. The new NCI Clinical Trials Network will require scientific priorities to be established by member groups that exploit their complementary strengths. In the common ground represented by AYA Oncology, the potential of this Network to advance clinical trials across pediatric and adult cooperative groups could not be greater. If

successful, this effort could serve as a paradigm for expanding AYA-focused collaboration in Europe and elsewhere internationally.

Pediatric cooperative oncology groups are positioned to play leadership roles in establishing such intergroup collaborations, and there are several reasons why this can be expected to be productive. First, as one cooperative group with international membership, the COG has demonstrated that dedicating resources to AYA Oncology leads to more study of these cancers [11–17]. Second, C10403 is the first AYA-focused intergroup study of ALL collaboratively developed by both pediatric and medical oncologists. Data being collected concurrently on C10403 and the pediatric trials AALL0232/AALL1131 will permit novel comparisons of survival and toxicity outcomes on a common regimen delivered in the adult versus pediatric settings, as well as drug delivery of key agents and psychosocial determinants of care. Discussions have begun concerning future AYA-focused partnerships between the COG and SWOG, providing a model that can be replicated in other countries. Finally, AYA Oncology has emerged as a priority at the level of federally funded cancer research in both the United States [19] and Canada [20,21]. All of these factors suggest that expanded intergroup collaborations in AYA Oncology are realistic in the United States and elsewhere.

In pursuing AYA-focused intergroup collaborations, three categories of studies are envisioned. Studies addressing typical pediatric cancers that occur less commonly in adults and where expertise resides in the pediatric group should be the primary responsibility of the pediatric group. In contrast, studies addressing typical adult cancers that occur less commonly in children where expertise resides in the adult group should be the primary responsibility of the sponsoring adult group. Studies addressing cancers distributed broadly across the AYA age range where expertise resides in both groups would be best developed as true intergroup efforts. For all studies, it is anticipated the intergroup relationship will facilitate cross-group entry of eligible patients.

Details of proposed intergroup collaborations can be specified only with knowledge of policies and procedures specific to the sponsoring organizations, agencies, and countries. Nonetheless, the successful research experience of the COG AYA Committee and others, maturation of the AYA Oncology discipline itself, and mechanisms such as the new NCI Clinical Trials Network have converged to create notable opportunities for clinical trials and biology research in this arena.

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