Collaboration is key to bridging the AYA cancer care divide

Sharon Worcester

A range of efforts and collaborations aim finally to correct the disparities in survival improvements among adolescents and young adults with cancer.

Survival gains among adolescents and young adults (AYAs) with cancer continue to lag behind outcomes for children and older adult patients. It's a trend that spans decades, but clinicians and researchers are finally getting serious about trying to understand the underlying causes and are re-examining prevailing practices in an effort to address the discrepancies.

"This is a very heterogeneous group of disorders," Rabi Hanna, MD, a pediatric hematologist and oncologist at Cleveland Clinic Children's Hospital, Ohio, said in an interview. He's specifically referring to the cancers that affect AYAs, who are broadly defined as patients aged 15 through 39 years. "A few cancers, such as [acute lymphoblastic leukemia], are more common in children, and others, such as breast cancer, are more common in adults. The biology may be different in the adolescent and young adult patients, which may lead to different outcomes."


DR HANNA

In addition, the psychosocial needs in this age group differ vastly from those in other groups. "Many of these patients are in college or have just started their families, so we have to pay more attention to [issues related to] financial toxicity and fertility, for example," said Dr Hanna, who is the director of pediatric bone marrow transplantation at the clinic. (The term "financial toxicity" describes the cumulative negative impact of the high cost of care, lost work time, and delays in reaching educational and career goals on patients with cancer and their families.)

Another factor that likely contributes to the outcome disparities between AYAs and other populations with cancer is the relative lack of clinical trial involvement among AYAs.

A recent series of articles published in the journal Blood addressed these and other issues, among them, whether AYAs with acute lymphoblastic leukemia (ALL)[1] or aggressive B-cell non-Hodgkin lymphomas (NHLs) [2] should be treated as children or adults; treatment strategies for those with acute myeloid leukemias (AMLs); [3] management of Hodgkin lymphoma;[4] and psychosocial challenges and health-related quality of life (QoL) in AYAs with hematologic malignancies.[5]


DR CORTES

In the introduction to the series, Jorge Cortes, MD, an assistant editor on the journal, wrote that hematologic malignancies in AYAs "represent a unique challenge because of their special biological features and distinctive therapeutic requirements, as well as the unique medical, social, and psychological characteristics of this patient population."[6]

He noted, however, that "not much has been done to explore unique molecular and biological features of AYA hematologic malignancies. The discussion on the management of AYAs often centers on whether these patients should be treated in a pediatric setting or an adult setting, or with regimens designed for children or for adults," noted Dr Cortes, professor and chair of the chronic myeloid leukemia section in the department of leukemia at the University of Texas MD Anderson Cancer Center, Houston.

Therapeutic options: pediatric or adult protocols?

In their article on ALL in AYAs, Nicolas Boissel, MD, and André Baruchel, MD, note that the use of "fully pediatric protocols" in patients aged 15 through 20 years is supported by findings from numerous studies. In young adults, evidence increas-

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ingly supports "pediatric-inspired or even fully pediatric approaches" because they have been shown to significantly improve outcomes, with long-term survival rates nearing 70%.[1] Patients in these age groups require specific programs that factor in access to care and to trials, an increased risk of acute toxicities, and treatment adherence, which can be particularly problematic in AYAs, they concluded.

However, Kristen O'Dwyer, MD, and colleagues, argue in an article on AML treatment in AYAs that neither the pediatric nor adult approaches are ideally suited for AYAs because of the "distinguishing characteristics of AYAs with AML." Rather, they conclude that AYA-specific approaches merit consideration.[3]

Similarly, Kieron Dunleavy, MD, and Thomas G Gross, MD, note in an article on managing aggressive B-cell NHLs in AYAs that there is a "remarkable divide" in the treatment of patients younger than 18 years with lymphoma compared with their young adult counterparts, and that it underscores the need for collaboration in developing consensus regarding treatment of AYAs.[2]

Clinical setting: pediatric or adult?

Consideration is also being given to the clinical setting in which AYA patients receive their treatment. Lori Muffly, MD, MS, and colleagues have reported that survival was superior for AYA patients with ALL who were treated in pediatric cancer settings,[7] and other researchers have reported similar findings.

However, those improved outcomes in the pediatric setting might be offset by a higher use of resources and therefore higher costs, based on recent findings in a Canadian study by Paul C Nathan, MD, and colleagues.[8] Among 1,356 patients aged 15-17 years who were diagnosed with cancer between 1996 and 2010, the authors found that the cost of care was higher when treatment took place in a pediatric setting compared with in an adult institution, and that it was driven in part by higher hospitalization rates and longer hospital stays. These findings were true across different diagnoses, including leukemias, lymphomas, sarcomas, and germ cell tumors, but only during the initial treatment phase.

In an accompanying editorial, Helen M Parsons, PhD, and her co-authors wrote that adolescents who receive treatment in the pediatric setting "tended to seek more [emergency department (ED)] care immediately before diagnosis and during the initial treatment phase; these adolescents also used more home care services during initial treatment and survivorship.[9] They pointed out that the findings of higher inpatient days in the pediatric setting was not surprising given that induction therapies for pediatric ALL tend to be more complex and intensive than therapies commonly used in adults with ALL, and that pediatric cancer hospitals tend to have a wider array of services, including psychosocial and family support services.

"What is less clear is why individuals seen in pediatric settings have higher rates of ED care directly before diagnosis and during the initial treatment phase," they wrote, adding that further investigation was needed on this topic to better understand those trends. "The finding that adolescents treated in pediatric institutions had higher resource use across diagnostic groups demonstrates that resource utilization may be driven just as much by care setting as diagnosis."[9]

The authors of the editorial emphasized that because of the differences in health care delivery and payment structures between the United States and Canada, where the Nathan study was done, it was important that similar studies are done in the United States to confirm these findings.

Disease and developmental biology

As Dr Hanna noted, biological differences and changes over time suggest that different age groups need varying approaches to treatment and that they may have different outcomes with the same treatments.

For example, the biology of AML is known to change with age, Dr O'Dwyer and her colleagues noted,[3] citing a recent European study of 5,564 patients with de novo AML that showed that the frequency of favorable cytogenetics was low in infants (13.7%), increased in children (25%) and young adults (44%), and decreased again in middle age and older patients.[10]

"Most unfavorable cytogenetic abnormalities are rare across all age groups, though complex cytogenetics are relatively more frequent in infants, decrease in frequency in AYAs, and then increase in frequency beyond AYA," Dr O'Dwyer and her colleagues wrote.[3] It was also becoming more apparent that age influences the presence of AML-related molecular abnormalities, and recognition of age-related differences in disease biology "will provide the best opportunity to improve the clinical outcomes that have been static for decades."

Dr Boissel and Dr Baruchel also noted in their report that light was finally being shed on the "black hole" of understanding ALL biology in AYAs, and research has shown that there is a continuum between childhood and adult ALL.[1] They concluded that "risk stratification based on recent biology findings and sequential [minimum residual disease] evaluations should now be implemented, as well as new therapeutic options including immunotherapy and targeted therapies, at best within the setting of integrated pediatric and AYA protocols."

Psychosocial factors

"Cancer is a non-normative event for AYAs. It is extremely disruptive to them physically, psychologically, and vocationally ... and this poses significant challenges," John Salsman, PhD, director of clinical research in AYA oncology at Wake Forest University, Winston-Salem, NC, said in an interview.

These patients have 5-year survival rates that haven't improved in tandem with those in pediatric and adult populations over the last 3 decades, and in addition to the financial toxicity and strain, they also have higher rates of depression and anxiety, including fear of recurrence, he added. "Quality of life is incredibly important, and these things need to be addressed because of the developmental changes AYAs are navigating; there are issues of positive body image, family and career decisions ... these are challenging for anyone, and when you throw a cancer diagnosis into the mix they become disproportionately so."


DR SALSMAN

In a 2014 study, Dr Salsman and his colleagues found that AYAs with cancer had poorer physical and emotional quality of life when compared with matched controls, but better social quality of life.[11] The latter finding was surprising and highlights the importance of the social dimension in the lives of AYAs. "Patient after patient will say 'I found out who my real friends are,' " he said. "There's this refinement and deepening of the social network among some posttreatment survivors."

Dr Salsman and his colleagues are using those findings to develop interventions that can maximize self-care in posttreatment survivorship – a time when AYAs may feel they have a new lease on life and may be more motivated to adhere to recommendations and take care of themselves. For example, a randomized controlled pilot study that incorporates social media apps and other technologies to build on the positive social components of their lives in promoting physical activity interventions is underway.

Another intervention targets emotional well-being through the use of web-based tools to increase positive affect. A proof-of-concept study showed that the approach was feasible and well received, and a larger-scale randomized controlled trial is being planned, he said.

Dr Salsman also praised the PRISM (Promoting Resilience in Stress Management) tool developed by researchers at Seattle Children's Hospital. It was created to help AYAs with cancer and other illnesses learn coping skills to manage stress after their diagnosis and to boost quality of life beyond treatment. A digital app has also been developed to be used in conjunction with the program.

Trial enrollment

In his editorial introducing the Blood series on AYAs and cancer, Dr Cortes noted a paucity of clinical trials specifically designed for this population. "At the time of this writing, I could identify four therapeutic trials registered at www.clinicaltrials.gov that appeared to be somewhat specifically designed for AYAs (some included children also)," he wrote, describing AYA enrollment in clinical trials in cancer as "suboptimal at best."[6]

Dr Salsman said these dismal enrolment numbers could in part be related to treatment setting. Data suggest that most AYAs with cancer are treated in community-based practices rather than comprehensive cancer centers where the bulk of research is being done, he explained.

Dr Hanna agreed that more research involving AYAs was needed as is a better understanding of why enrollment is so much lower in this population. He pointed out that in 2017 the American Society of Clinical Oncology and Friends of Cancer Research released a statement recommending that pediatric patients be considered for enrollment in later-phase trials for cancer types that span both adults and children.[12] The organizations said that individuals aged 12 years and older should routinely be included in such trials because their drug metabolism is similar to adults, and inclusion of younger patients may also be appropriate if they are part of the population affected by the disease, depending on specific disease biology, action of the drug, and available safety information.

Officials at the Food and Drug Administration are considering that possibility, Dr Hanna said.

Dr Salsman added there has been an increase in recent years in the attention paid to disparities in survival improvements and trial involvement among AYAs with cancer, compared with other age groups. For example, about 5 years ago, the National Clinical Trials Network formed a working group that developed a number of specific objectives for incorporating more AYAs into cancer trials and finding better ways to study this population;[13] the Institute of Medicine held a forum on the care of AYAs with cancer;[14] and the National Cancer Institute held a state-of-the-science meeting that focused on identifying strategic priorities for AYA oncology,[15] he noted.

Dr Hanna added that "scientific groups such as Southwest Oncology Group (SWOG) and Children's Oncology Group (COG) also have AYA committees now. One of the success stories of working together between SWOG and COG was the intergroup study C10403 for patients with ALL. And now there are efforts for an intergroup AYA-AML task force to include representatives from each of the cooperative groups that historically coordinated myeloid disease clinical trials – COG, SWOG, Alliance, and ECOG-ACRIN," he said.

In fact, all of the National Clinical Trials Network groups have some initiative in place to address AYA concerns, said Dr Salsman, who chairs the ECOG-ACRIN AYA oncology subcommittee.

Despite these efforts, and many others, long-term survival improvements among AYAs with cancer still fall short, compared with those of other age groups.[16]

Next steps

Among the recommendations from authors in the AYA series in Blood is a call for assessing AYA-specific therapy in future clinical trials, as well as improved collaboration between adult and pediatric teams and the involvement of multidisciplinary teams in care for this population.

Many centers are already working on models for collaborative care, Dr Salsman said, citing the Fort Worth AYA Oncology Coalition led by medical director Karen Albritton, MD, as an example of a program that has been successful in helping clinical and supportive caregivers and their AYA patients "have a shared vision" as they work to maximize improvements in outcomes.

Patients are also taking the lead in demanding better care and attention to their psychosocial needs, Dr Hanna said. In the case of the community-powered advocacy organization Critical Mass, members have succeeded in getting lawmakers to introduce a bill in the US House of Representatives that would allow college students to defer loan payments while undergoing cancer treatment.

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