Introduction to a review series on adolescent and young adult malignant hematology

Hematologic malignancies occurring in adolescent and young adults (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. Unfortunately, not much has been done to explore unique molecular and biological features of AYA hematologic malignancies. The discussion on the management of AYAs frequently 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. Clinical trials specifically designed for AYAs are scanty. At the time of this writing, I could identify 4 therapeutic trials registered at www.clinicaltrials.gov that appeared to be somewhat specifically designed for AYAs (some included children also). Enrollment of AYAs in clinical trials in cancer in general has been suboptimal at best. AYAs are a group of individuals that are somewhat loosely and heterogeneously defined. Most frequently, they are defined by age with boundaries that vary in different reports. An accepted definition, one supported by the National Cancer Institute in the United States, includes those individuals between the ages of 15 and 39 years. Worldwide, individuals age 15 to 39 represent ~40% of the total population. According to the National Institutes of Health, among individuals age 15 to 39 years, ~70,000 new cases of cancer are diagnosed every year, representing ~5% of all cancers diagnosed in the United States. The incidence of cancer in general has increased from 2000 to 2011 in the ages of 20 to 34 years, a period during which the incidence has declined for those aged 50 years or older. Lymphomas and leukemias are among the 10 most common invasive cancer diagnoses in AYAs according to SEER (Surveillance, Epidemiology and End Results) between 2000 and 2011, with lymphoma at number 4 (incidence 6.9 per 100,000) and leukemia at number 10 (2.7 per 100,000) in females, and at numbers 2 and 8, respectively, in males (incidence 7.7 and 2.8 per 100,000, respectively). This translates into a significant number of deaths related to hematologic malignancies in AYAs. In the United States, in 2015, 518 male and 318 female AYAs died of leukemia, representing the second and fifth most common cancer-related deaths during that year in this age group. An additional 236 males died of non-Hodgkin lymphoma (the fourth most common cause of cancer-related death). In other parts of the world, the situation is similar. In Latin America, for example, lymphomas and leukemias represent the second and third most common cancers in male AYAs between 1998 and 2007, accounting for 17.5% and 12.1% of all cancers in this group. In females, they represent the third and fifth most common cancers, constituting 12.1% and 7.4% of all cancers during this same time period.

In this review series, we explore the current status and challenges of hematologic malignancies in AYAs. The series underscores our current knowledge and also points to the multiple gaps existing in knowledge and management of this patient population. Boissel and Baruchel discuss the biological variability of acute lymphoblastic leukemia (ALL) in AYAs in what they describe as the “biological continuum between childhood and adult ALL.” This analysis reflects not only our new understanding of the molecular heterogeneity of ALL, but also the complexity of this patient population at the molecular level. They also analyze the treatment options for AYAs, as well as the role of stem cell transplantation and the approach to specific subtypes such as patients with ALL with the Philadelphia chromosome. Finally, they review the available data and possible role of monoclonal antibodies and chimeric antigen receptor T-cells in AYA patients. O’Dwyer, Freyer, and Horan do a similar analysis for acute myeloid leukemia (AML) in AYAs. They discuss the molecular heterogeneity of AML and how this differs in older and younger patient populations. They also discuss the difference in approaches using pediatric and adult regimens in a disease where much remains to be improved with either strategy, including the role of transplantation in these patients, emphasizing the need for more AYA-specific trials and data. This review also discusses other important aspects such as the aforementioned low enrollment of AYAs in clinical trials and the survival end points in AYAs in different series from various parts of the world.

In the review on non-Hodgkin lymphomas, Dunleavy and Gross discuss the variable subtype distribution in AYAs compared with other age groups and underscore the paucity of molecular data in this area. The one entity for which AYAs have been more prominently studied is primary mediastinal B-cell lymphoma, where, as pointed out by the authors, a large majority of patients are AYAs. The review analyzes the contrast between therapeutic strategies in pediatric patients, where Burkitt lymphoma and diffuse large B-cell lymphoma are treated similarly with excellent results, and adults, for whom different regimens are typically used. Flerlage, Metzger, and Bhakta discuss the current status of Hodgkin lymphoma in AYAs, a group that represents a majority of all patients affected by this entity. Considering the significant cure rate for patients afflicted with Hodgkin lymphoma, this review discusses the shifting focus on late effects and the way this has affected recently the design of treatment strategies. As with other entities, a discussion on the need to enroll more AYAs in clinical trials is an important topic of this review. Finally, Husson,
Huijgens, and van der Graaf discuss the various psychological and health-related quality-of-life aspects that are unique to this patient population. The review addresses psychological challenges as varied as, among others, peer and family relationships and the very difficult but real end-of-life discussion. Other important aspects such as the need for a multidisciplinary team, the importance of the design and setup of the facilities, and the training of the health-care professionals who care for these patients are also discussed.

In this series, we present the following reviews that we hope you will find informative and stimulating:

- Nicolas Boissel and André Baruchel, “Acute lymphoblastic leukemia in adolescent and young adults: treat as adults or as children?”
- Kristen O’Dwyer, David R. Freyer, and John T. Horan, “Treatment strategies for adolescent and young adult patients with acute myeloid leukemia”
- Kieron Dunleavy and Thomas G. Gross, “Management of aggressive B-cell NHLs in the AYA population: an adult vs pediatric perspective”
- Jamie E. Flerlage, Monika L. Metzger, and Nickhill Bhakta, “The management of Hodgkin lymphoma in adolescents and young adults: burden of disease or burden of choice?”
- Olga Husson, Peter C. Huijgens, and Winette T. A. van der Graaf, “Psychosocial challenges and health-related quality of life of adolescents and young adults with hematologic malignancies”

We hope you will enjoy this series, that it can be a spark that stimulates research in hematologic malignancies in this patient population, and that it can ultimately be of service to the care of these patients and lead to improved outcomes in all aspects of their care.

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REFERENCES