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LYMPHOID NEOPLASIA

Comment on Wadhwa et al, page 221

Poverty and health equity in childhood leukemia

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In this issue of *Blood*, Wadhwa et al describe findings from a Children's Oncology Group (COG) study indicating a 1.9-fold greater hazard of relapse among children undergoing maintenance treatment for acute lymphoblastic leukemia (ALL) and living in extreme poverty.[1]

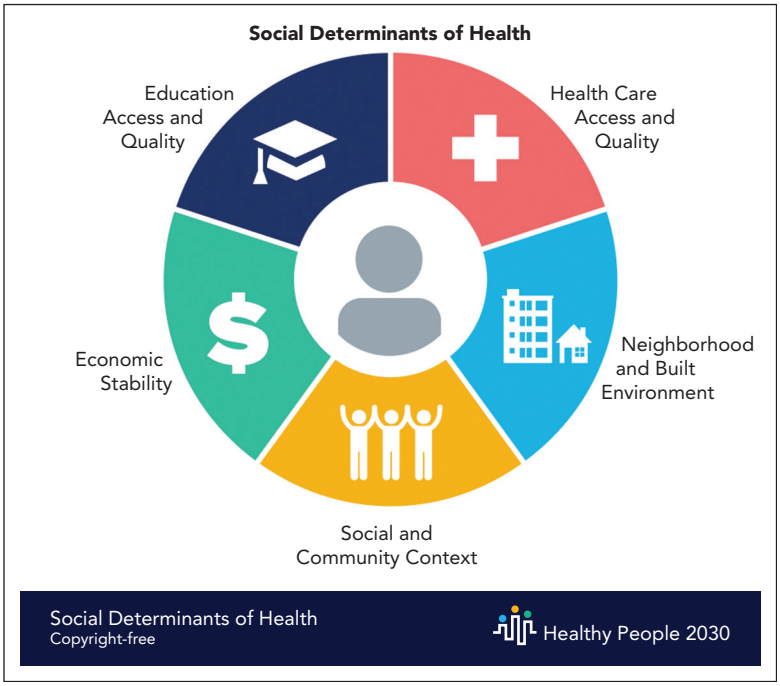
Although a relatively rare disease, childhood cancer is emblematic of the remarkable progress that can be made through multi-institutional cooperation and a standard practice of approach for enrollment to clinical trials. In the United States, where over 60% of eligible children and young adults aged <29 years enroll to cancer clinical trials, the 5-year overall survival of childhood ALL has increased from <25% in the 1960s and 1970s to >90% today.[2] However, the global majority of children do not benefit from this remarkable progress, so that childhood cancer survival remains neither equal nor equitable by geographic region, socioeconomic status, or demographic group. For example, although cancer survival in the United States now exceeds 80%, the 5-year overall survival of childhood cancer in 3 African low- and middle-income countries remains <40%.[3] In the United States, Hispanic and Black children treated for B-cell ALL across 8 COG clinical trials experienced inferior overall survival compared with children who are White or Asian.[4] Social determinants of health (see figure) include individual and neighborhood/community factors, infrastructure, and approaches taken to governance and public policy and are increasingly recognized as major contributors to health risks and outcomes.

Poverty is a key social determinant that affects 1 in 5 children living in the United States: Hispanic and Black children are 1.5- to 2-fold more likely to live in poverty than children who are White, non-Hispanic.[5] The profound health implications of poverty are supported by the markedly poorer outcomes experienced by Medicaid-insured adolescents and young adults diagnosed with cancer, particularly those who experience interruptions in coverage that may affect access to care.[6] The impact of parental socioeconomic status on childhood ALL outcomes was recently summarized in a meta-analysis indicating a 17% to 33% increase in death rates among children with ALL and less favorable area-based socioeconomic status indexes.[7] Subsequent to this analysis, work conducted within the Dana Farber consortium also demonstrated a higher risk for early ALL relapse and inferior survival among children living in high-poverty areas, as defined by zip code.[8] At present, factors related to socioeconomic status and related barriers to health care access are not routinely incorporated in childhood cancer risk assessment or decisions related to treatment approach.

The work presented by Wadhwa et al is significant because so few studies to date have investigated poverty as an individual-level risk factor for adverse outcomes in childhood cancer.

The study team leveraged survey and clinical data collected from a COG adherence study to examine associations between self-reported household income and risk for relapse in childhood ALL. For this analysis, classification of participants living in extreme poverty was arbitrarily defined as those living 120% below the federal poverty threshold, comprising ~12% of the overall cohort. Despite limitations of sample size, the key finding of this work is a hazard of relapse among children living in extreme poverty that is nearly twice that of children not living in extreme poverty, after adjusting for established prognostic factors. Although the extreme poverty subgroup was less likely to achieve a previously defined critical adherence threshold to oral mercaptopurine, importantly, adherence status did not attenuate the relationship between extreme poverty and relapse.

Clinicians who treat children diagnosed with ALL have long understood that "favorable" disease features are insufficient to ensure survival, and, for many cases, factors underlying a heightened risk for relapse remain frustratingly elusive. It is quite possible that social constructs such as poverty play as important a role in disease prognosis as do age, cytogenetics, and response to therapy. The answer to this question is not yet clear, given that end-induction minimal residual disease, the single most powerful predictor of relapse in childhood ALL, was not available to the study team for inclusion in their analysis. Nevertheless, these observations provide a foundation for future study and identify a unique opportunity to address and confront a novel prognostic factor that is potentially modifiable. Indeed, a pilot study recently demonstrated feasibility and acceptability of a targeted, scalable intervention that delivers groceries and provides transportation to at-risk families of children recently diagnosed with cancer.[9] At minimum, the results described by Wadhwa et al



Social determinants of health. Reprinted from the US Department of Health and Human Services.[10]

provide valuable insight on the potential impact of poverty on ALL outcomes and support the comprehensive, longitudinal collection and analysis of social determinants of health data in childhood cancer clinical trials in the context of well-established prognostic indicators, with the hope of informing future intervention strategies.

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Kanapuru et al, page 235

Equality: trial and error?

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In this issue of *Blood*, Kanapuru and colleagues[1] describe that specific eligibility criteria in trials in multiple myeloma (MM) may lead to underrepresentation of Black patients due to failure to meet hematology laboratory- and treatment-specific requirements.

The authors reviewed clinical trials in MM submitted to the US Food and Drug Administration (FDA) for drug approval, including ethnicity and reasons for screen failure. Similar to a recent systematic review analyzing all randomized clinical MM trials conducted over the past 15 years, they found a low representation of non-White patients (17%), with only 4% being Black.[2] The present study, which comprised nearly 9500 patients, is unique for its focus on identifying the reasons behind ineligibility for study participation. Its objective was to identify opportunities for narrowing racial disparities that exist in clinical trials. The study found that Black patients had the highest overall ineligibility rate at 24%, compared with 17% in White patients and 11% in Asian patients. The primary reason for this disparity was that fewer Black patients met hematology laboratory criteria, potentially due to an inherent lower hemoglobin level and neutrophil count. Additionally, the authors suggest that limited access to standard care led to a higher percentage of Black patients who failed to meet treatment-specific eligibility criteria. This lack of access would disqualify them from participating in trials that increasingly require patients to have undergone a certain number of prior therapies, with different mechanisms of action and demonstrated refractoriness to multiple drugs.