ED in APL: tip of the iceberg?

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Park et al report in this issue of Blood that, despite the results reported in major clinical trials, the rate of early death (ED) in acute promyelocytic leukemia (APL) found in a population-based study remains high over the past 15 years. 

Based on data obtained from the US Surveillance, Epidemiology, and End Results (SEER) registry, the authors show that the ED rate for APL is not only considerably higher than that described in clinical trials (ie, 17% vs 3%-10%), 

and that it has not been affected significantly by the advent of modern treatment with all-trans retinoic acid (ATRA). Given the rarity of APL (0.2-0.3 cases/100,000/year) the total number of cases represents a meager figure. However, because of the reasons detailed below, the issues raised by this article are relevant for hematologists, oncologists, and health care providers in general.

First of all, we are dealing with a highly curable malignancy. Once regarded as the most aggressive and rapidly fatal human leukemia, APL has become over the past 2 decades the most frequently curable leukemia, with more than 80% of patients now being long-term survivors after combinatorial regimens including ATRA and anthracycline-based chemotherapy. However, it is extremely important that patients are managed in highly specialized and experienced units. 

Early death, mainly because of hemorrhage, and disease relapse account for most failures currently reported in clinical trials. 

Given the above-mentioned therapeutic achievements, ED presently represents, together with disease relapse, the major obstacle to further increasing the cure rate of APL patients. In fact, the impressive progress with antileukemic therapy to decrease the relapse rate has not been paralleled by similar advances in reducing ED. This report by Park et al is therefore very appropriate and timely.

In terms of ED reporting, it may be that clinical trials only describe the tip of the iceberg. It is unclear at present what percentage of patients diagnosed with APL are in fact referred to specialized care. Unfortunately, this information is not available in the study by Park et al. Together with another recently reported population-based study carried out in Sweden, the article by Park et al strongly suggests that the rate of ED in APL is unexpectedly much higher than commonly believed, indicating that this number must be revised, taking into account real-world data. As suggested in both of these articles, more investigation and education are warranted to better address the issue. 

We also believe that a better definition of ED and, particularly, an appropriate distinction of distinct ED types (before and during induction therapy) and causes of death (hemorrhage, infection, differentiation syndrome, etc.) are needed to better identify factors with a relevant impact on each failure type.

It seems clear that ED in APL should be categorized in several distinct groups: (1) death before diagnosis (unrecognized although strongly suspected cases); (2) death because of misdiagnosis and/or inappropriate therapy; (3) pretherapy death in bona fide APL cases; and (4) death during induction therapy. As a first step, agreement is also needed on an adequate ED definition in terms of time frame. This definition should encompass all deaths occurring from the period before therapy initiation up to the end of induction (which may occasionally last more than 30 days!) as defined by morphologic complete remission coupled with complete hematologic recovery. Lack of precise definitions will inevitably generate confusion and difficulties in interpretation. To define ED as that occurring within 20 or 30 days is meaningless and incorrect. Furthermore, deaths occurring before and after the commencement of therapy should be analyzed separately because distinct factors likely affect them. Some examples include disease characteristics, delayed diagnosis, and late referral to specialized units that may impact significantly on pretherapy. Some additional factors such as exacerbation of the coagulopathy during therapy, infection related to treatment, and differentiation syndrome may also account for induction death. One of the limits of their study acknowledged by Park et al is the lack of information on the causes of death that was unfortunately not available in the SEER dataset.

One simple action to better establish the size of the problem could be to request that authors of clinical trial studies report in detail all relevant information for patients who were excluded from the study because of eligibility criteria. This could be stimulated by reviewers and editors requesting these data. With very few exceptions, these data are omitted from clinical trial reports. In parallel, epidemiologic registries should be encouraged to collect more information on patient history and causes of death, and a greater effort should be made in general to foster population-based studies such as the ones conducted by Park et al1 and Lehmann et al. 

To conclude, it is important that the generalized sense of optimism on APL curability fostered by results with modern treatments be tempered by the notion that the disease remains highly fatal if not promptly recognized and adequately treated in highly specialized institutions. This article by Park et al is a timely and useful warning in this respect. A combined effort of epidemiologic studies and improved education tailored to health caregivers to increase awareness and expertise in this leukemia should result in diagnosing more cases, conveying to appropriate management, and ultimately saving more human lives.

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REFERENCES
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Susceptibility to childhood leukemia

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Leukemia occurs as the result of leukemia-promoting factors and the ability/inability of the immune system to attack and eliminate upcoming malignant cells. In this issue of Blood, Almalte et al describe in a case-control study how the presence of activating killer-cell immunoglobulin-like receptors (KIRs) reduces the risk of childhood leukemia.1

“Why me?” is a common question of families with children diagnosed with leukemia and we usually have no satisfying answer. Childhood leukemia is thought to be associated with genetic factors, and investigators have focused on leukemia-promoting factors in the past. However, the development of leukemia could not only be a result of malignant cell growth but also depend on the ability/inability of the immune system to attack and eliminate the initial malignant cells. In a candidate gene approach a novel association between activating KIR genes and childhood leukemia provides insights concerning pathogenesis of childhood leukemia and has implications for developing new immunotherapies for this cancer.1

KIRs are a group of receptors expressed on natural killer (NK) cells and T-cell populations. KIRs belong to the Ig-superfamily and consist of type 1 transmembrane glycoproteins with 2 or 3 Ig-like domains and possess either a short (activatory KIR) or long (inhibitory KIR) cytoplasmic tail. The overall KIR repertoire is determined by the KIR genotype and the decision as to which KIRs are expressed on each NK cell is regulated by the methylation of KIR gene loci. KIR receptors specifically bind HLA class I molecules (HLA-A, -B, and -C) and structurally it has been shown that KIRs bind the peptide-binding region of HLA. The ligands of activatory KIRs are believed to belong to stress-induced, viral, or tumor proteins. Unlike T cells, which respond to foreign peptides on HLA molecules, NK cells attack cells that are “missing self,” that is, lacking

Childhood leukemia is thought to be associated with genetic factors, and investigators have focused on leukemia-promoting factors in the past. However, the development of leukemia could be a result of the inability of the immune system to attack and eliminate upcoming malignant cells (A). In the presence of KIR genes, the risk of childhood leukemia is reduced because of a possible attack of leukemia cells by NK cells or T cells (B). Inheriting a higher number of activating KIR genes (> 4) is associated with significant reductions in risk for ALL in children (C).
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