HBV might exploit 2 different mechanisms for causing either indolent (mixed cryoglobulinemia) or highly malignant (DLBCL) B-cell lymphoproliferative disorders. In the case of DLBCL, HBV infection of B cells may enhance overall mutagenesis (possibly through APOBEC enzymes) and alter B-cell–specific signaling pathways (possibly through AID). Among the latter, alterations in the FOXO pathway might result in lymphomagenic tonic B-cell receptor signaling. DLBCL cells do not seem to express stereotyped idiotypes putatively recognizing HBV antigens. Conversely, in mixed cryoglobulinemia, continual antigenic stimulation by HBV may drive the clonal expansion of B cells expressing specific stereotyped idiotypes that regress upon suppression of infection by antiviral therapy. There is no evidence suggesting the possibility of progression from mixed cryoglobulinemia to DLBCL.

HBV-related DLBCL in Chinese patients.[8] This large predominance of DLBCL over indolent lymphoproliferative disorders supports a model of HBV-driven mutagenesis directly leading to DLBCL rather than that of stimulation-driven progression from indolent to aggressive forms. HBV-driven mutagenesis might occur by a hit-and-run mechanism, because Ren et al could not detect any HBV DNA integrated into DLBCL cells. Nevertheless, the continual antigenic stimulation model still stands as the most likely explanation for HBV-dependent mixed cryoglobulinemia (see figure).

The large body of data from Ren's study provides a framework for deciphering the mechanisms by which HBV alters the B-cell genome up to development of DLBCL and, importantly, identifies potential therapeutic targets for these aggressive tumors. Future studies should clarify whether the distinctive molecular signatures found in HBsAg+ DLBCL Chinese patients are also present in patients of Western origin. In addition, the issue of whether virus-specific stereotyped idiotypes may be involved in some HBV-associated monoclonal

lymphoproliferative disorders[2,7] should be further addressed.

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TRANSPLANTATION

Surviving childhood cancer: a sobering story

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Childhood cancers account for <1% of all cancers diagnosed, which amounts to ~157 000 new cases annually. The table shows the common types of cancer and percentage of occurrence; leukemia and brain tumor account for more than half of all childhood cancers. In this issue of *Blood*, Holmqvist et al report on the long-term survival of 362 survivors of childhood cancer who were in continuous remission and alive 2 years after autologous hematopoietic cell transplantation.[1]

Overall, there was a 23-fold increase in late mortality compared with that in an age- and sex-matched general population. Recurrent primary disease was the predominant cause of mortality in the first 10 years after transplantation and the cause for half of all deaths in their cohort. The 2 other major causes of late mortality were a second cancer and infection, each accounting for ~20% of deaths.

In children, autologous transplantations are reserved for high-risk solid tumors (as consolidation therapy) and for Hodgkin and non-Hodgkin lymphoma. Because the study population in Holmqvist et al dates back to 1980, about 25% of transplantations were for acute lymphoblastic or myeloid leukemia. Because autologous transplantations are no longer offered for

acute leukemia in children, subset analyses that excluded childhood survivors of acute leukemia were undertaken; the analyses confirmed that the risks for late mortality were consistent with those observed for the whole cohort. Although mortality rates decline in those who survive for more than 10 years, the numbers of patients are substantially fewer. Studies that include an adequate number of very long-term survivors are needed to understand the risks of late mortality in these survivors.

A recent report on late mortality from Canada observed that 25% of long-term survivors of autologous transplantation suffered a later death (death occurring >2 years after transplantation).[2] Yet there are differences between the reports. In

Common types of childhood cancers and percent occurrence

Type	%
Leukemia	30
Brain and spinal cord tumors	26
Neuroblastoma	6
Wilms tumor	5
Hodgkin lymphoma	3
Non-Hodgkin lymphoma	5
Rhabdomyosarcoma	3
Retinoblastoma	2
Bone cancers	3

Based on data from the American Cancer Society (https://www.cancer.org/cancer/cancer-in-children/types-of-childhood-cancers.html).

the Canadian report, recurrence of the primary malignancy accounted for almost 90% of deaths, and the risk of late mortality was 700-fold higher compared with that in an age- and sex-matched population. The differences between the 2 reports are not easily explained but they support the conclusion that substantial numbers of children with neuroblastoma in continuous complete remission 2 years after autologous transplantation remain at risk for relapse and late mortality. Despite advances in the treatment of neuroblastoma and the continued improvement in survival, life-long surveillance is needed for early detection of recurrent neuroblastoma. However, the rigorous implementation of life-long surveillance is challenging. Children transition to adulthood and with that transition comes changes in their personal providers, which may include transition of care from a pediatric oncologist to a general internist; loss of insurance coverage for health care for some; and for others living away from home, a genuine underappreciation of the need for continued surveillance. Although tumors of the central nervous system account for ~25% of childhood cancers, there are few long-term survivors, which underscores the need to improve upon current treatments for these tumors. The 2 other major causes of late mortality observed in the report by Holmqvist and colleagues were second cancer and infection. The risk of mortality from recurrent disease plateaued at about 10 years after transplantation, but the risk of mortality from nonrelapse causes

(infection and second cancer) continues for more than 2 decades. This is more in keeping with the risk reported in adults after autologous transplantation, primarily for Hodgkin and non-Hodgkin lymphoma.[3] Children are sometimes heavily pretreated with high-dose radiation, and second cancer as a cause of late mortality is expected. However, what is interesting is the rather high proportion of late deaths attributed to infections without concurrent primary disease. Although the authors were unable to explain their observation, it is plausible that immune reconstitution is delayed for several years in heavily treated children. Although aggressive surveillance is recommended, immune reconstitution after chemotherapy and autologous transplantation is not well studied. Future research that focuses on immune reconstitution after aggressive chemotherapy may prove insightful.

Second cancer is a devastating complication of the treatment of the original cancer. This may occur as a result of chemotherapy with or without high-dose irradiation before autologous transplantation or as a result of the transplantation procedure. Broadly, second cancers can be classified into 3 groups: (1) therapy-related myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML); (2) lymphoma, including lymphoproliferative disease; and (3) solid tumors. Therapy-related MDS or AML is common after autologous transplantation, a major cause of nonrelapse mortality.[4] Its incidence can range from 1% to 25%, and risk factors include both pretransplant and transplant-specific characteristics.[5,6] Pretransplant risk factors include exposure to alkylating agents, topoisomerase II inhibitors (epipodophyllotoxins and anthracyclines), or high-dose radiation. Transplant-specific risk factors include use of peripheral blood instead of bone marrow grafts, peripheral blood stem cell mobilization with etoposide, low number of CD34$^+$ cells infused, transplant conditioning with total body irradiation, and multiple transplants.[4] The latency period to therapy-related MDS or AML after topoisomerase II inhibitors is shorter (<5 years) compared with that for alkylating agents or irradiation (4-7 years). Lymphoma and solid tumors are typically seen after allogeneic transplantation.

In summary, survivors of childhood autologous transplantation need life-long monitoring for late and very late complications.

Clinicians who provide care for transplant survivors should be aware that survivors are generally at greater risk for mortality and, in particular, high rates of late infections and respiratory (infectious and noninfectious) complications.[7] This can be achieved only by continuously educating survivors and their families and through guidelines for surveillance that are easily available to general pediatricians and general internists. It is noteworthy that published guidelines generally address complications by organ and in the context of transplantation. It would be worthwhile for pediatric oncologists to develop cancer-specific surveillance guidelines that address surveillance for recurrence in addition to organ damage.

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