Nonhepatic Cancer in the Pediatric Liver Transplant Population: Guidelines From the ILTS-SETH Consensus Conference

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Abstract. The incidence and geographical distribution of cancers in children are dramatically different from the adult population. Consequent to improvements in postcancer survival, there is a progressive increase in the number of patients requiring liver transplantation (LT) who are in remission from pretransplant malignancy (PTM). Conventionally, however, PTM has been considered a relative contraindication to LT. Furthermore, with improving post-LT survival now extending beyond decades, the cumulative effect of immunosuppression and the increasing risk of de novo cancers need to be acknowledged. A working group was formed to evaluate, discuss, and retrieve all the evidence and provide guidelines with regards to best practices surrounding nonhepatic cancer in the pediatric LT (PLT) population. Further subsections of research included (a) extrahepatic solid tumors, leukemia, lymphoma, and other hematological disturbances before PLT and (b) malignancies following PLT (including posttransplant lymphoproliferative disorders). This guidance provides a collection of evidence-based expert opinions, consensus, and best practices on nonhepatic cancers in PLT.

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INTRODUCTION

Pretransplant malignancy (PTM) in remission has conventionally been considered a relative contraindication to liver transplantation (LT).[1,2] There remain concerns that immunosuppression could potentially increase risk for an early recurrence of the index cancer, making LT futile. Consequent to dramatic improvements in postcancer survival, there is a progressively increasing number of patients requiring LT who are in remission from PTM.[3,4] Furthermore, with improving post-LT survival now extending beyond decades, the cumulative effect of immunosuppression and the increasing risk of de novo cancers needs to be acknowledged. With most data being archaic and based out of voluntary databases, guidelines for diagnosis, LT indications, prevention, and treatment of nonhepatic cancer in LT need reevaluation.

Within the International Liver Transplantation Society and The Spanish Society of Liver Transplantation consensus conference, a working group consisting of experts was formed to evaluate, discuss, and retrieve all the evidence and provide guidance on best practices surrounding nonhepatic cancer in the pediatric LT (PLT) population. Further subsections of research included extrahepatic solid tumors, leukemia, lymphoma, and other hematological disturbances before PLT and malignancies following PLT (including posttransplant lymphoproliferative disorder).

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The methodology is reviewed in detail in the introductory article.[5]

EPIDEMIOLOGY

The incidence and geographical distribution of cancers in children are dramatically different from the adult population.[3] Childhood cancer is the sixth leading cause of total cancer burden globally and the ninth leading cause of childhood disease burden globally.[3,6,7] A substantial portion of the global burden of childhood cancer exists in low, low-middle, and middle sociodemographic index countries (82.2% of the global childhood cancer burden). These include countries in Asia, Africa, and Central and South America. This geographical pattern of cancer burden distribution is noticeably different from that observed in adults, with only 50.3% of the global adult cancers burden affecting these countries.[3,6,7]

Based on the estimates by the Global Burden of Disease 2017 Childhood Cancer Collaborators, the prevalence of childhood cancers is much lower than that of the adult population. Cancers in the first 2 decades of life represent only 1% of the annual cancer incidence in the United States. However, it was highest in the 0- to 4-y age group and contributed to 37% of the global 0- to 19-y childhood cancer absolute disability-adjusted life years burden.[3,6,7] Leukemias (34.1%) constituted the highest proportion of categorized childhood cancers, followed by brain and nervous system cancers (18.1%).[3,7,8]

Over the past 30 y, the survival rate in children and adolescents with cancer has steadily improved and the cancer-specific death rate has decreased by >50%. Presently, 8 out of every 10 children and adolescents diagnosed with cancer survive 5 y or more beyond their diagnosis.[3,4,7,9] It is estimated that the number of years of life saved by the successful treatment of childhood cancer exceeds all other cancers when compared with adults. The current 5-y survival rate is nearly 80%, ranging from 39% to 97% within age- and diagnosis-specific groups, with the overwhelming majority of these patients being cured of their original malignancy.[4,9] Nonetheless, it is sobering to realize that the vast majority of these cancer survivors will have at least 1 chronic health condition by 40 y of age.[4,9,10] Survivors of childhood cancer are at risk for serious, disabling, life-threatening, or fatal treatment-related late effects including organ failure. Data including those from the United Network for Organ Sharing and Childhood cancer survivor study databases show that the incidence of children undergoing LT with a PTM is low and ranges between 0.77% and 1.5% of the whole PLT population.[4,11,12]

Recommendations

- The profile of malignancies in adults and children are very different with regards to incidence, type, and geographical distribution. *(Strength of recommendation: Strong; Level of evidence: High)*
- There has been a steady improvement in the survival of children with pediatric malignancies, with long periods of remission. These children and adolescents are at risk for treatment-related late effects including organ failure. (*Strength of recommendation: Strong; Level of evidence: High)*
- Incidence of pretransplant malignancies is low among the pediatric population. *(Strength of recommendation: Strong; Level of evidence: Moderate)*

INDICATIONS

Unlike the adult population, indications for PLT in childhood cancer survivors are multifactorial and most often related to the index cancer.[4,11,12] These include a primary genetic predisposition like transient abnormal myelopoiesis leading to liver failure and leukemias in children with Trisomy 21.[13] Children with hematological malignancy have a predilection to developing primary liver dysfunction or acute liver failure due to cancer or other cancer-associated pathology like hemophagocytic lymphohistiocystosis.[14] Other indications of PLT in this cohort include those related to the treatment of primary cancer. These may include therapeutic modalities like radiation and chemotherapy-related liver dysfunction and those related to hematopoietic stem cell transplant, transfusion-related hepatitis, or iron overload.[4,9,11,15] Other causes like TPN-related cholestatic liver disease, graft versus host disease, and veno-occlusive disease also constitute indications of PLT in children with PTM.

Recommendations

- Indications for LT in children who have nonhepatic malignancy are multifactorial and are usually the consequence of pretransplant malignancy (PTM) or its treatment. (*Strength of recommendation: Strong; Level of evidence: Moderate)*

TIMING OF LIVER TRANSPLANTATION

Literature related to the latency between a PTM and PLT is very limited. Data have largely been extrapolated from adult LT or other SOTs.[1,2] In the pediatric population, Shah et al[12] reported a higher and earlier incidence of post–heart transplantation malignancy in patients transplanted with PTM. The risk of recurrence was however lower (2.7%–13.8%) after pediatric liver or kidney transplant in highly selected patients.[16,17] The "ideal" latency period between cancer resolution and transplantation remains undefined.

It does, however, seem reasonable to indicate PLT only when the oncological probability of survival of the PTM disregarding immunosuppression is at least 50% at 5 y.[18] Beitinjaneh et al[8] showed that waiting for at least 6 mo dramatically improved post-LT survival in patients with PTM (62.5% versus 22.25%). There are also some data to suggest that prolonging the wait time for transplantation for potential recipients with PTM may result in worse outcomes after LT.[4,9,11] Hence, for selected survivors with severe organ dysfunction, PLT may offer the best chance for extended survival. The potential benefits and risks must be evaluated on an individual basis. Life-saving LT should not be absolutely contraindicated in carefully selected pediatric patients where LT may be performed before the stipulated latency period.[8,11,19,20] Moreover, a series from

the United States and the United Kingdom show that curative treatment of PTM before LT reduces the risk of recurrence.[8,19] The caveat in these cases is that the PTM should be amenable to sustained remission before LT and there should always remain the option of post-LT adjuvant therapy. Such a scenario is more often observed in hematological malignancies. Living donor LT, especially in regions where pediatric deceased donor LT programs are not active, allows for timely availability of liver allografts. This permits optimal timing of the LT and avoidance of delays between the end of chemotherapy and LT.[14,21]

Recommendations

- No prespecified waiting period recommendation can be made for children with PTM, provided that at the time of consideration, there is an oncological survival probability of 50% at 5 y. *(Strength of recommendation: Strong; Level of evidence: Moderate)*
- Sustained remission of the PTM before LT reduces the recurrence rate and allows for future chemotherapy. *(Strength of recommendation: Strong; Level of evidence: Moderate)*
- Living donor liver transplantation provides a valuable alternative with excellent results in children with PTM because it allows optimal timing for LT, minimizing any delay between completion of chemotherapy and planned LT. *(Strength of recommendation: Strong; Level of evidence: Moderate)*

DE NOVO MALIGNANCIES FOLLOWING PEDIATRIC LT

An increased risk for cancer after LT is well established. Moreover, dramatic improvements in survival after PLT have resulted in a potential life expectancy even greater than in adults, leading to more prolonged exposure to immunosuppression.[22-24] The role of immunosuppression in muting the native immune system's antitumor action along with the immaturity of the immune system and the pretransplant seronegativity to oncogenic viruses such as Epstein-Barr virus (EBV) make the PLT a particularly vulnerable group.[22,23,25] Consequently, there is a significantly higher cancer incidence and mortality than age-matched nontransplant patients. Overall, the long-term risk of cancer among pediatric solid organ transplant (SOT) recipients (SOTRs) is 12–33 times greater than the general population.[22,23,25,26] Moreover, the cumulative incidence of cancer increases with the time elapsed after SOT (from 7%, by 10 y, to 13%–15% by 20 y and 26%–41% by 30 y posttransplantation).[22,23,25,26] In the Nordic series, 22% of the cancers occurred within 2 y of LT, 38% occurred at 2–9 y, and 41% occurred beyond 10 y after LT.[27] In contrast to adults, cancer types other than lymphomas, such as oropharyngeal, biliary, pancreas, and lung cancers, were rare in patients <20 y. In adults, the risk of cancer is markedly modified by patient-specific factors such as age, history of alcohol abuse, smoking, and transplant indication. In PLT recipients, these risk-modifying factors are often absent and, when present, are different from those of a typical adult LT recipient.[15,24-26,28] Nonetheless, with increasing life expectancy, the burden of immunosuppression-associated comorbidities increases, as do the environmental and other risk factors for de novo malignancies (DNMs).

There, however, remains a paucity of data regarding malignancy following PLT. DNMs account for 5%–16% of nonhepatic-related deaths after PLT and together with cardiovascular complications are a major cause of late death after LT.[15,23] In children, the risk of developing DNMs is 19-fold higher than adults, emphasizing the pressing need for strategies to reduce cancer risk, which may include cancer surveillance recommendations especially specific to young adult transplant recipients in the process of transition of care.[15,23,25,26,29] This particular cohort of recipients will also likely benefit from earlier onset of adult-specific cancer surveillance and care.

Recommendations

- The risk of developing post-LT DNMs in children is several-fold higher than the general pediatric population. This post-LT risk is also higher than adults *(Strength of recommendation: Strong; Level of evidence: Moderate)*
- Posttransplant lymphoproliferative disorders (PTLDs) are the most frequent DNMs in children after LT. *(Strength of recommendation: Strong; Level of evidence: High)*

POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDERS AND EPSTEIN-BARR VIRUS

Although significant variation exists between study populations, PTLDs are the most common oncological diseases following SOT in children, representing >50% of all malignancies.[22-25,29] The risk of developing non-Hodgkin's lymphoma is >200 folds in pediatric SOTRs as compared to the age-matched general population.[4,24-26] The risk is amplified in the youngest recipients, who are more likely to be seronegative for EBV at transplantation. Moreover, pediatric SOTRs are also at significantly higher risk of nonmelanoma skin cancer and other solid cancers, which often manifest late after transplant.[4,24-26]

Incidence of PTLD varies between 1% and 20% depending on the organ transplanted, the type and intensity of immunosuppression, and pretransplant immunological status of EBV. The highest rates of PTLDs have been reported among intestinal (20%) and lung and cardiac (10%) recipients with lower incidence for liver and kidney recipients (2%–5%), reflecting the higher degree of immunosuppression and greater presence of allograft lymphoid tissue in the organs with the highest incidence of PTLDs.[26,30-32]

Typically, EBV-positive PTLD appears early after transplant, with the highest incidence occurring in the first year after LT.[25,30,31,33] The transmission of EBV to the recipients may occur via the passenger leukocytes from an EBV seropositive organ donor. Such a passage via the allograft along with an immature immune system allows for relatively easy transmission and high incidence of EBV-positive PTLDs in the initial months following post-LT. Other sources of transmission of EBV include nonleukodepleted blood products and typical community-acquired exposures.[24,30,31]

Due to the presence of maternal antibodies, evidence of EBV exposure is difficult to establish in infants. It is, therefore, prudent to consider seropositive infants as seronegative for the purpose of EBV prophylaxis. Nonetheless, a determination of recipient and donor EBV serological status is important for risk stratification. Also, the peak EBV viral load along with an increasing trend in the titers acts as a reliable surrogate marker for predicting early PTLDs.[33-36] Thus, close monitoring of EBV DNA may be helpful in the early diagnosis and treatment of PTLDs in pediatric LT recipients. Monitoring EBV DNA levels may be of value in higher-risk recipients, with frequencies ranging weekly in the first 6 mo after LT to monthly thereafter for at least the first year.[36,37] A definitive diagnosis of PTLDs is made by tissue histopathology, which should further be tested for EBV and CD20 status.[30,34-36] PTLD cases should be classified using the World Health Organization 2017 classification system for tumors of hematopoietic and lymphoid tissues.[38] This classification divides PTLDs into 4 categories: nondestructive PTLDs, polymorphic PTLDs, monomorphic PTLDs, and classic Hodgkin's lymphoma PTLD and allows for treatment and prognostic stratification of these lesions.

A complete staging workup includes strategies similar to those used for lymphoma staging in immunocompetent patients.[30,38,39] These include imaging of the chest, abdomen, and pelvis. The need for neuroimaging in patients without neurological symptoms is uncertain. However, many centers recommend performing an magnetic resonance imaging brain as initial workup due to its importance in prognosis and treatment.[30,31,33,39]

Recommendations

- Close blood monitoring of EBV DNA is crucial in the early diagnosis and treatment of PTLDs. *(Strength of recommendation: Strong; Level of evidence: Moderate)*

TREATMENT OF PTLDS

Survival post-PTLD is very good and is greater in children than adults.[26,40,41] Low histological grade and an early diagnosis are predictors of excellent outcomes.[26,37,40,42] Reduction or cessation of immunosuppression remains the first-line treatment in the algorithmic management of EBV/PTLD.[30,37,40,42,43] This strategy is based on the hypothesis that recovery of the host's immune system allows the cytotoxic T lymphocytes to act against EBV and consequently control EBV-driven B-cell proliferation. Success of this treatment strategy is usually clinically evident within 2–4 wk of initiating immunosuppression reduction.[30,37,40,42,43] Nonetheless, up to 35% of patients with PTLDs fail to remit with this strategy either due to tumor unresponsiveness or significant rejection. Moreover, reduction of immunosuppression is unlikely to be effective against PTLD lesions that behave more like true malignancy and are no longer under the control of EBV.[30,42,43] Rituximab is now considered standard therapy for most $CD20^+$ PTLDs resistant to immunosuppression reduction (including polymorphic and monomorphic diffuse large B-cell lymphomas subtypes).[30,35,37,40] Further standard treatment regimens in PTLDs unresponsive to reduction of immunosuppression or rituximab include sequential treatment with 4 cycles of rituximab followed by 4 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy.[30,40,44-46] Antiviral therapy (acyclovir and ganciclovir) inhibits lytic EBV DNA replication in vitro. However, a majority of EBV-infected cells within PTLD lesions are transformed B cells independent of the EBV, and hence, antivirals are unlikely to play a role in the direct treatment of PTLDs.[37,40,42,47] Complete or partial surgical resection, as well as local radiotherapy, has been used as adjunctive therapy and should be only reserved for residual localized tumor and as salvage therapy.[30,40,44]

Recommendations

- Post-PTLD survival is better in children than adults. There is an excellent response to minimizing immunosuppression, and it remains the mainstay of treatment of PTLDs in children. *(Strength of recommendation: Strong; Level of evidence: High)*
- The treatment of PTLDs requires an algorithmic approach. Nonresponse to minimizing immunosuppression in 2–4 wk should be escalated to monoclonal antibodies (rituximab) or chemotherapy. *(Strength of recommendation: Strong; Level of evidence: High)*

STRATEGIES TO PREVENT DE NOVO MALIGNANCY

Multiple strategies have been designed to minimize or modify immunosuppression to decrease the risk of DNMs.[24,25,31,33,40] These are detailed elsewhere in the consensus reports. In brief, usage of mammalian target of rapamycin inhibitors (mTORi) is a specific type of immunosuppression with antiproliferative and immunosuppressive effects. In pediatric transplant recipients, the use of mTORi is mostly based on clinical data obtained from adults. Notably, 2 randomized trials comparing mTORi with standard-dose calcineurin inhibitors raised concerns about a possible risk of PTLDs in children receiving mTORi immediately after kidney and LT.[48-50]

Treatment of DNMs in pediatric transplant recipients mirrors the general population approach to the same malignancy. As adolescents with PTM transition to adult follow-up, early institution of cancer screening and prevention practices as outlined in the consensus documents is strongly encouraged.

FUTURE TRENDS

The field of biomarkers is an area garnering a lot of interest. These markers are important when the tumor is a nonsecretor with regards to conventional tumor markers. Potentially a simple blood test can help in the diagnosis, prognostication, and management of cancers, a modality termed as "liquid biopsy."[51-53] Detecting circulating tumor cells (CTCs) is one such tool that enables the assessment of treatment completeness. Epithelial cell adhesion molecule–positive CTCs in the peripheral blood have been shown to demonstrate a significant association with advanced disease and shorter overall survival. Studies including those from Germany showed that the positive predictive

value of CTC detection for tumor *recurrence* was 89%, even when the lesion was untraceable by current imaging techniques.[54,55]

Circulating cell-free DNA (cfDNA) is a short fragment of double-stranded extracellular DNA that is released into the bloodstream by tumor apoptosis or dead cells and is found in many types of cancers.[56-58] The development of next-generation sequencing has allowed this modality to mature into one of clinical importance. The levels of circulating cfDNA drop back to normal when a tumor is completely removed. Hence, the levels of postoperative circulating cfDNA correlate with the presence of microscopic residual disease. Therefore, postoperative circulating cfDNA helps identify the high-risk group for malignancies and has potential as an excellent monitoring tool, but more data are required before widespread use can be advocated.

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