11.1 Introduction

The concept of tumor was first put forward by Thomas in 1959 [1]. The hypothesis was that the immune system is an active process controlling the emergence of malignant clones from somatic cells during the lifetime of a normal, immune-competent individual. The increased incidence of cancer observed in patients with immune deficiencies compared to the general population strongly supports this hypothesis [2, 3]. The cause of such immune deficiencies may be a genetically inherited defect, secondary to human immunodeficiency type 1 (HIV-1) infection, or iatrogenic following solid organ transplantation (SOT) or hematopoietic blood or marrow transplantation (BMT).

Retrospective surveys of patients with primary and secondary immune deficiencies have revealed an increased risk for specific cancer types. Lymphoproliferative disorders are much more common than observed in immune-competent children and represent the majority of cancers in immunocompromised children. De novo, reactivated, or chronic infections play a pivotal role in promoting the development of lymphoproliferative disease observed in children with immunodeficiency. Patients with primary (genetically determined) or secondary (acquired) immune deficiencies, which primarily affect T-cell function, are at the highest risk of developing lymphomas, often associated with Epstein-Barr virus (EBV). Primarily due to the growing number of transplants, it is estimated that over 150 cases of EBV-associated lymphoproliferative disease (EBV-LPD) are diagnosed in children in the USA each year [4]. This compares to the approximately 750 cases of childhood non-Hodgkin lymphoma (NHL) diagnosed per year in the USA [5], including 300 cases of Burkitt lymphoma, 200 cases of lympho-
blastic lymphoma, 100 cases of anaplastic large cell lymphoma, 100 cases of diffuse large B-cell lymphoma, and 50 unspecified cases of NHL [6].

In addition to lymphomas, patients with secondary immune deficiencies are at increased risk for carcinomas that are linked to infection with viruses such as human herpes virus-8 (HHV-8) and human papilloma virus (HPV). Additionally, not all lymphomas are associated with infectious agents, such as EBV. Therefore, the defect in immune surveillance may be in identification and/or elimination of cells with abnormalities of proliferation, function, and/or apoptosis; and more than just the inability to properly control infections.

In general, children who are immunodeficient and develop a malignancy, including lymphoma, have a worse prognosis compared to other individuals with histologically similar malignancies. For children who develop a localized NHL, the outcome can be quite favorable after surgery with or without radiation therapy. However, many lymphomas in this population are disseminated and require systemic cytotoxic therapy. These patients usually tolerate cytotoxic therapy poorly, with increased morbidity and mortality secondary to infectious complications and end organ toxicities. The overall goal of therapy is to enhance immunity, i.e., reduction of immunosuppression in transplant recipients, effective antiviral therapy for HIV-1-infected patients or immune replacement with hematopoietic stem cell transplantation in patients with a primary immunodeficiency. If these results can be achieved, then there is a better chance of achieving remission and decreasing the risk of recurrence. In this chapter, we will focus on advances made in our understanding of the etiology, pathogenesis, and the treatment of lymphomas in this unique population of patients that are being increasingly cared for by pediatric oncologists.

11.2 Epstein-Barr Virus

Epstein-Barr virus (EBV) is clearly associated with much of the lymphoproliferative disease observed in immunodeficient children. EBV is one of eight known human herpes viruses and is subgrouped into the gamma herpes virus subfamily. Like all herpes viruses, EBV is able to persist in the host for life, but in the vast majority of healthy carriers, the virus causes no disease. As will be discussed later in this section, disruption of the fine balance between the host immune system and the virus may lead to the development of EBV-related disease. The only natural host for EBV is man. EBV infects B lymphocytes and squamous epithelium of the oral and nasopharynx. EBV initially infects B cells in lymphoid tissue of Waldeyer's ring [7, 8]. These B cells may remain latently infected. Latently infected B cells may disseminate throughout the body as resting memory B cells in secondary lymphatic organs, i.e., lymph nodes, spleen, and bone marrow [9], and become the reservoir for EBV infection [10]. The number of latently infected B cells is approximately $10^{-5}$ to $10^{-6}$ of all B cells, and this number remains stable for most of the life of the individual [10, 11]. If viral reactivation and replication occur, then cell lysis and death with shedding of the virus into the saliva occurs. The outcome of salivary EBV is either horizontal transmission to another host or infection of the oronasal epithelium resulting in virus replication, which then can infect other B cells.

Latent infection is characterized by the expression of nine virally encoded proteins: EBNA-1, EBNA-2, EBNA-3A, EBNA-3B, EBNA-3C, leader protein (LP), latent membrane protein (LMP)-1, LMP-2A, and LMP-2B [12]. EBV-encoded RNAs (EBERs), EBER-1 and EBER-2, are seen in all latently infected cells, but they do not code for any proteins, and their function has not been determined. Expression of EBV genes varies among the spectrum of EBV-associated diseases and often differs from in vitro immortalized lymphoblastoid B-cell lines (LCL) or normal human resting B cells infected by EBV [13, 14]. Briefly, EBV-positive Burkitt lymphoma cells commonly express only EBNA-1, EBER-1, and EBER-2, which defines type I latency. Type I latency is also observed in a portion of EBV-positive gastric carcinoma. Type II latency, as defined by EBNA-1, LMP-1, LMP-2, EBER-1, and EBER-2 expression and is found in EBV-positive nasopharyngeal carcinoma, T-cell NHL, and the Reed-Sternberg cells of some patients with Hodgkin lymphoma. The EBV-LPD-infected cells observed in immunodeficient patients resemble in vitro immortalized LCL and generally express all nine EBV-related latent proteins (type III latency). It has been shown that peripheral resting