Therapeutic strategies and indications of Radiotherapy (RT) in EBV related lymphoproliferative disorders

Opinion

The Epstein-Barr virus (EBV) is a member of the gamma-herpesvirus family and is also called human herpesvirus-4. It is recognized as the first virus to be directly implicated in carcinogenesis. The EBV is widespread in nature, may be reactivated by immunodeficiency and is divided into two subtypes (EBV-1 and EBV-2) that differ in geographic distributions and the organization of the genes encoding EBV nuclear antigen. The EBV-1 is more prevalent and relatively more efficient in terms of transforming infected-B cells. The EBV-2 is detected specially in the equatorial Africa, New Guinea and Alaska. It is now known that EBV infects more than 90% of the world’s population and the primary infection typically occurs in childhood. The vectors are saliva, oral contact and rare cases of transmission by transfusion. During acute infection, EBV primarily infects and replicates in the stratified squamous epithelium of the oropharynx. This is followed by a latent infection of the B lymphocytes and upon primary infection the individuals become a life-long carrier of the virus without any serious sequel. After that EBV will be present, as both latent and replicating virus, and in most healthy individuals it is generally asymptomatic. It is important to note that in healthy individuals both humoral and cellular immune responses are evoked by primary infection of EBV. Although the precise role of EBV in oncogenesis is currently poorly understood, the presence of the virus in all tumor cells suggests its implication in development of solid tumors and hematologic malignancies. EBV must maintain its viral genome in the cell to be carcinogenic, but avoid killing it by preventing the cell from being a potential target of the immune system. The virus must also activate the pathways of cellular growth. The EBV genome is maintained in B lymphocytes, either as a multicopy circular episome or by integrating the viral DNA. The EBV latent genes induce an activated phenotype in the infected B cells and, despite these cells have been not transformed, if they proceed to unchecked or acquire oncogenic mutations, they can become neoplastic years after primary EBV infection. Lymphoproliferative disorders (LPDs) and malignancies such as nasopharyngeal carcinoma, Burkitt’s lymphoma, and Hodgkin’s disease can emerge from a clone of EBV-infected cells.

T-cell LPDs that have been reported to be EBV-associated include a subset of peripheral T-cell lymphomas, angioimmunoblastic T-cell lymphoma, extranodal nasal type natural killer/T-cell lymphoma, and other rare histotypes. The association of EBV and LPDs is systematic classified, taking into account clinical characteristics, features of morphology; immunology, cytogenetics, and molecular genetics. The antivirals currently in clinical use (anti-herpes virus and anticytomegalovirus agents) have a moderate anti-EBV effect, maintaining its viral genome in the cell to be carcinogenic, but avoid killing it by preventing the cell from being a potential target of the immune system. The virus must also activate the pathways of cellular growth. The EBV genome is maintained in B lymphocytes, either as a multicopy circular episome or by integrating the viral DNA. The EBV latent genes induce an activated phenotype in the infected B cells and, despite these cells have been not transformed, if they proceed to unchecked or acquire oncogenic mutations, they can become neoplastic years after primary EBV infection. Lymphoproliferative disorders (LPDs) and malignancies such as nasopharyngeal carcinoma, Burkitt’s lymphoma, and Hodgkin’s disease can emerge from a clone of EBV-infected cells.

Proteasome inhibitors when combined with radiation therapy, leads to p53-mediated apoptosis. The combination also showed synergic effects in locally advanced non-small cell lung cancer, by decreasing homologous recombination and expression of genes (BRCA1, FANCD2 and RAD51) known to be associated with radioresistance. Despite no definitive radiation dose schema defined in the literature, a report by Barron et al. examining the feasibility and effectiveness of radiation therapy in patients with LPD was published. A group of 14 patients was evaluated and 85% of the patients were immunocompromised. The indications for radiotherapy (RT) included acute neurologic dysfunction from local progression in the brain and spine, airway compromise and obstructive hepatopathy. Median RT dose was 24 Gy (range 8-36 Gy). With a median follow-up of 7.9 months, locoregional control was achieved in 90% of patients tested the effects of the combination of histone deacetylase and proteasome anti-EBV activity. So the combination of induction of EBV lytic phase therapy with subsequent exposure to anti-herpes virus drugs can be used to increase the therapeutic ratio. EBV can promote oncogenesis through different paths: preventing apoptosis, deregulating the cell cycle, suppressing and degradation pro-apoptotic tumor suppressors by proteasome. The therapeutic effects of targeting anti-apoptotic mechanisms remain unexplored, but increasing evidence indicates that the ubiquitin-proteasome system plays an important role in cancer development. Ubiquitination is a post-translational modification that plays a role in several cellular processes including cell cycle progression, cell proliferation, DNA replication, degradation and apoptosis. Several tumor suppressors and oncogenes interact with enzymes of the ubiquitin-proteasome pathway that function in ubiquitin conjugation and deconjugation. EBV can manipulate the function of ubiquitin-proteasome system that is indispensable for the survival and replication of the viruses in the infected cells. Proteasome inhibitors inhibit cell growth and promote cell death in a variety of cancers and several possible mechanisms of the anti-cancer effects mediated by proteasome inhibitors. The first proteasome inhibitor approved by FDA was Bortezomib. Since 2003 the treatment of multiple myeloma and mantle cell lymphoma could include this drug.
inhibitors on the apoptosis endemic Burkitt lymphoma lines and lymphoblastoid cell lines, providing a rationale for the use of histone deacetylase and proteasome inhibitors, opening a path for futures studies combining these immunomodulators with RT, as the apoptotic effects were dependent on reactive oxygen species generation. In conclusion, despite increasing evidence of the potential role of EBV in EBV-associated LPDs there is still no unified targeted therapeutic strategy established. Immunotherapeutic approaches have shed new light in LPDs therapy, but it is necessary to consider the innate immunity in controlling both: infections and tumors. RT plays a hole on focal symptoms relief as a result of disease progression, in special in cases of Immunocompromised patients, but new immunological targets linked particularly to NK cells, and new less toxic radiation modalities should be exploited with therapeutic purposes.

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Conflict of interest

The author declares there is no any conflict of interest.

References