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Burkitt's Lymphoma

Introduction

Burkitt's Lymphoma is the most common childhood cancer in Africa, with an annual incidence of 6 per 100,000 children and peak incidence at 8 years of ageⁱ. Although there are three classifications of Burkitt's lymphoma (endemic, sporadic, and immunodeficiency-associated), endemic Burkitt's Lymphoma (eBL) is by far the most common, primarily being found in equatorial Africa and other developing countries. Sporadic and immunodeficiency-associated (usually found in patients with HIV/AIDS) are more common in developed countries, but are a lesser public health concern because of their relatively low prevalence; the prevalence of Burkitt's Lymphoma in Africa is estimated to be fifty times that in the USⁱⁱ. From a public health standpoint, the primary concern is to improve early access to treatment of eBL in resource poor areas where prevalence of this childhood cancer is high. Barriers to successful treatment include access to facilities equipped to diagnose and treat eBL, the cost and supply of drugs, availability of trained personnel, and high rates of complicating infections due to immunosuppression.

Background

eBL is a malignant tumor caused by oncogenic mutation of B lymphocytes. Typically, this cancer presents as a solid tumor involving facial bones, most commonly the jaw. As the tumor progresses, the molar teeth begin to loosen and eventually become

displaced. The tumor may also arise in other locations, such as the kidneys, gastrointestinal system, ovaries, and breastⁱⁱⁱ. The progression of this cancer rarely includes the bone marrow (7% of cases), but involvement of the central nervous system is more common (19% of cases) and is associated with higher morbidity and mortality^{iv}. It should be noted that although eBL is a lymphoma, it is atypical in that presents it in extra-nodal sites as a solid mass as opposed to increased leukocytes in blood and lymph.

Burkitt's lymphoma was first identified by Denis Burkitt in 1958^v. While living in equatorial Africa, he noted an unusually high number of children who presented with rapidly growing facial masses, typically involving the jaw. The prevalence of these tumors was found to be concentrated in areas of lower altitude, which led Burkitt to postulate that some arthropod vector was associated with development of this tumor. Gilbert Dalldorf first made the association of eBL prevalence with malaria transmission, suggesting that *Plasmodium falciparum* (the parasite causing malaria) was involved in the pathogenesis of eBL^{vi}.

A unique hallmark of eBL is its association with early infection by the Epstein-Barr Virus (EBV), a type of herpesvirus. Within the lymphoma belt (the region of equatorial Africa with high prevalence of eBL, including countries such as Uganda and Kenya) over 95% of cases of eBL show evidence for EBV infection of tumor cells. Outside of the lymphoma belt there is a slightly weaker correlation. eBL tumors in Northern Africa are positive for EBV in 85% of cases^{vii}. The role of EBV is not as clear in the other two sub-types of Burkitt's Lymphoma that are predominantly found in developed countries, which are classified as sporadic or immunodeficiency-associated. Only 15–20% of sporadic Burkitt's lymphoma present with EBV infection^{viii}.

EBV plays a role in the pathogenesis of various other cancers, including non-Burkitt's B-cell lymphomas, T-cell lymphomas, Hodgkin's disease, nasopharyngeal and gastric cancer. It is known to cause infectious mononucleosis if exposure first occurs during adolescence^{ix}. The reason for the various clinical manifestations of EBV infection is not completely understood, but is likely influenced by the age of infection, environmental factors, nutritional status, and co-infections (such as malaria)^x.

Importance of epidemiology

The epidemiologic characterization of eBL has made an enormous contribution to our current understanding of how cancers develop. Of particular importance was the discovery of the role of viral DNA insertions in mutation rates. Understanding interactions between malaria, the immune system, EBV, and oncogenesis is key to understanding how to develop treatment programs and target vaccines.

The geographical distribution of eBL can be used to make treatment programs as efficient as possible. The relative infrequency of the disease and the specialized medical diagnostic and treatment facilities that are needed means that programs must be centralized. The challenge is then to have centrally located facilities that are able to serve a large region of rural villages that has a relatively high incidence^{xi}.

A hallmark of eBL is its association with prior EBV infection early in childhood, however, the mechanism behind this association is not completely understood^{xii}. African children are infected with EBV earlier in life than Americans and Europeans: 44% of African children are seropositive by the age of 12 months, 81% by 2 years and nearly

100% by 3 years^{xiii}. This coincides with the relatively high rates of infectious mononucleosis in the U.S. and Europe, but high eBL in Africa.

More recent studies have verified the initial observations made by Burkitt and Dalldorf that malaria transmission plays a role in the etiology of eBL, although variance in malaria transmission does not account for all of the variance in eBL^{xiv}. Immunologic studies support this relationship, showing that malaria infection alters the ability of the immune system to suppress EBV infected B lymphocytes, increasing the likelihood of tumorigenesis^{xv}. However, the mechanisms by which this occurs are not fully understood.

Since the prevalence of eBL cannot be attributed solely to rates of malaria transmission and EBV infection, further epidemiologic studies are needed to identify additional cofactors in the pathogenesis of eBL, including environmental and cultural factors. One area of active research is directed towards milkbush (*Euphorbia tirucalli*), a plant native to regions of Africa with particularly high rates eBL. This plant is used for both medicinal and recreational purposes and the sap is known to have tumor promoting properties^{xvi}. The tendency for males to have higher exposure to this plant may explain the 2:1 male to female ratio of eBL.

Barriers to Treatment

Since eBL is a rapidly proliferating tumor, it generally responds well to cytotoxic therapy. In developed countries with adequate resources, this translates to excellent cure rates – up to 90%^{xvii}. The normal chemotherapeutic regimen varies with the location of the tumor, but includes a combination of cyclophosphamide, doxorubicin, vincristine,

methotrexate, cytarabine, ifosfamide and etoposide. Treatment may also include steroids, monoclonal antibodies, such as rituximab, as well as bone marrow or stem cell infusions.

However, eBL is primarily a cancer of the developing world, where medical and financial resources are not as robust and cancer treatment programs face major difficulties. Barriers include access to facilities equipped to diagnose and treat eBL, the cost and supply of drugs, availability of trained personnel, and high rates of complicating infections due to immunosuppression. As with many other diseases of the developing world, the primary barrier to treatment is the direct cost. These costs include diagnostic laboratory tests (complete blood count, histopathology, X-ray, ultrasound, biochemistry) and cytotoxic drugs (normally a combination of cyclophosphamide, vincristine, and methotrexate) on top of any other medical costs. Typical pricing for these services (taken from Nigeria) is \$28.5 for laboratory tests, \$103.8 for cytotoxic drug regimen, and an estimated \$31.5 for all other medical costs^{xviii}. This is a total of \$163.80 to diagnose and treat a child with eBL, an extraordinary sum of money for a rural subsistence farmer. In one attempt to study program efficacy in Nigeria, only half of patients who sought treatment were able to afford therapy. 31.7% withdrew their children against medical advice, and 20% did not begin treatment. Some also opted for treatment without laboratory confirmation of eBL^{xix}.

Tumor stage upon presentation is a highly predictive of treatment outcome. Since eBL is a fast growing tumor, it is imperative to initiate treatment quickly. This is often difficult, since rural villages are long distances from any health facility, much less a hospital that is equipped to administer cytotoxic therapy. In the same Nigerian study, over half of patients presented with late stage disease^{xx}.

Even when adequate treatment is accessible and affordable, outcomes are not as positive as those in the developed world. Part of the reason for this is the increased risk of infection^{xxi}. During cytotoxic therapy, the immune system is severely weakened and patients are highly susceptible to infectious diseases. Lack of sterile conditions and high transmission rates of infectious diseases contributes to the elevated mortality seen in developing countries, despite adequate treatment.

Solutions and Successful Programs

Two steps can be taken to improve prompt access: 1.) educate health workers, as well as the general population, on how to identify BL. 2.) Establish referral networks between rural clinics and hospitals where treatment can be obtained. In addition, the cost of cytotoxic drugs must be reduced. This may be accomplished through donations from wealthier countries, adjusting regimens (monotherapy instead of combination), or policy changes in drug pricing.

One approach that has been suggested to achieve these goals is twinning between institutions in developed countries and institutions in underdeveloped countries, an approach that has been elaborated by Drs. Raul Ribeiro and Ching-Hon Pui

Briefly, twinning fosters interactions between public hospitals in developing countries and established cancer treatment centers, with the goal of improving survival rates among children with cancer. The best results have been obtained when local oncologists were recruited as program directors and asked to promote the idea of a strong pediatric oncology unit among their peers and coordinate the training of providers. Although at first the partner institution in the more affluent country may subsidize the costs of treatment, these and other expenses are eventually met with funds raised by charitable groups in the community. Such alliances have generated sufficient momentum to allow some hospitals in Central and South America to begin sharing their expertise with other oncologists in the developing regions of Latin America,

by developing joint treatment protocols and consulting about problems in the management of childhood cancer^{xxii}.

Most often, however, countries with eBL cannot afford to run these programs even at subsidized cost, but this does not exclude the possible benefits of twinning. “In parts of Africa, for example, it may be possible to cure children of Burkitt's lymphoma by treating them with cyclophosphamide alone, and there is evidence from Malawi that even a simplified twinning program can save lives. Thus, a modified program concentrating on education, training, and the treatment of the most responsive cancers could be quite effective.”^{xxiii}

This twinning has been implemented in Tanzania, where best estimates indicate about 700 children die of eBL every year^{xxiv}. The Interchurch Medical Assistance (IMA) World Health Program has developed a partnership with a local medical center, the Shirati Mennonite Hospital, which has led to a countrywide treatment program. This relationship has not only allowed for resources to be transferred from areas of prosperity to lower income regions, but has also facilitated the adaptation of treatment programs to the local environment.

Physicians at Shirati Mennonite Hospital have been developing a more affordable treatment regimen that is appropriate to the immediate situation. They have been able to design a regimen where one large IV dose of a chemotherapeutic drug is given, and within a few days the child is able to return home with a significant reduction in the tumor size. The child must then return for two follow-up injections 3 weeks apart, done on an outpatient basis^{xxv}. This cuts down the cost of drugs and reduces the burden of lengthy hospital stays. Although this appears to be a successful therapeutic regimen, no concrete data is available to support the efficacy of this intervention.

Shirati Mennonite Hospital, in conjunction with a medical advisor from the IMA, has become a central training location for the region. Medical personnel are trained in rapid diagnosis methods and treatment protocol. These personnel then staff 37 hospitals throughout Tanzania. Precursory data appears positive, but due to the limited staff and resources for the reporting of data in these locations, it is difficult to assess the effectiveness of these programs. In the past 3 years, 6 of the 37 hospitals have reported a total of 770 children treated for eBL, indicating that treatment is becoming more available^{xxvi}. It should be noted that these programs are highly dependent on outside resources; the IMA has donated chemotherapeutic drugs and medical supplies to help augment the cost of this program.

In Malawi, similar efforts have been made to reduce the cost of treatment regimens. A study in 2003 confirmed that a monotherapy regimen of cyclophosphamide could cure children with facial and abdominal BL, although it does not appear as effective as combination therapy and was dependent on the number of courses given. The survival rate was 63.5% in children with tumors restricted to the head, and 33.3% in children with the primary tumor involving the abdomen or other locations. Survivors had received an average of 6 courses, whereas non-survivors received an average of 4 courses^{xxvii}.

The Red Cross Children's Hospital in South Africa has also contributed to the development of new treatment protocols. Patients are stratified into one of three groups (A, B, or C) based on the stage and location of the tumor. Ideal treatments regimens have been established for each group, but in general, more intensive chemotherapy results in greater morbidity, but a significant reduction in mortality^{xxviii}.

Conclusions

Endemic Burkitt's Lymphoma is a significant cause of morbidity and mortality in many developing countries, particularly those found in the lymphoma belt of equatorial Africa. Access to medical facilities equipped to diagnose and treat eBL, the cost and supply of drugs, availability of trained personnel, and high rates of complicating infections all contribute to the difficulty of treatment. Twinning between institutions and novel approaches to treatment programs have been successful at reducing these obstacles, but much work remains to achieve integrated regional programs that can manage costs as well as effectively identify, diagnose, and treat the thousands of children who suffer this disease.

Useful Resources

<http://www.cancer.gov/cancertopics/types/non-hodgkins-lymphoma>
<http://www.virtualbloodcentre.com/diseases.asp?did=746>
http://www.who.int/vaccine_research/diseases/viral_cancers/en/index1.html

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