

Burkitt's lymphoma is a B-cell lymphoma that was initially described by Dr. Denis Burkitt in Uganda in 1958. Through his diligent observations, research, and the subsequent contributions of other pioneers in the field, Burkitt's lymphoma is now considered by some to be a model tumor secondary to its impact on the general understanding and treatment of lymphomas.¹ The study of Burkitt's lymphoma has also been groundbreaking in the understanding of viruses such as Epstein Barr virus (EBV) in having lymphotropic properties and carcinogenic potential.

There are three general subtypes of Burkitt's lymphoma worldwide. The first is the endemic form, which was originally described by Burkitt and which still is largely found in Africa and the tropics worldwide, affecting children primarily between the ages of two and nine. The sporadic form is largely found outside of Africa, primarily affects young adults, and often presents with abdominal masses. The third subtype is associated with HIV, and is found worldwide.² The endemic variant in particular is largely found within the "lymphoma belt," a region that extends from West to East Africa between the 10th degree north and 10th degree south of the Equator and continues south down the Eastern African coast.³ Interestingly, of the three variants of Burkitt's lymphoma EBV is most closely associated with the endemic variant, with nearly 95-100% association.^{4,5} The lymphoma, largely presenting as jaw tumors in African children, is exquisitely sensitive to chemotherapy, given its rapid rate of division. In fact, it is the fastest growing tumor known, doubling in size within 24 hours.⁶ While EBV has been scientifically implicated in the pathogenesis of African Burkitt's lymphoma, various articles have been published regarding the interplay between EBV and pathogens such as *Plasmodium falciparum*, mosquito-borne arboviruses, and even extracts from plants such as *Euphorbia tirucalli*.^{7,8}

The significance of Burkitt's lymphoma to cancer care in sub-Saharan Africa is important to recognize. Burkitt's lymphoma is the most common childhood cancer in equatorial Africa, accounting for 3000 deaths per year.⁹ Within available reported cancer registries in Africa, the incidence of Burkitt's lymphoma is highest in countries such as Uganda, where the Kyadondo County's cancer registry reports an age-standardized rate per 100,000 of 4.7 for boys and 3 for girls.² Given its great disease burden, there has been a

significant interest in therapeutic options to treat African children with Burkitt's lymphoma over the past 50 years, including the development of various collaborations between African institutions with Western healthcare systems. However, despite the many breakthroughs in treatment of this malignancy, many African children are still unable to access treatment. Many perish of their illness, despite the tumor's remarkable chemosensitivity, and with possibility of cure with even cheap chemotherapeutic regimens.

The evolution of treatment regimens

Various modalities of treatment for Burkitt's lymphoma in Africa have been attempted, with varying levels of success. While chemotherapy has been the cornerstone of treatment, after introduction of methotrexate in the 1960s produced rapid responses in African children with Burkitt's lymphoma, other treatment modalities were also researched. Radiation therapy was highly anticipated in the early 1970s, though achieved poor results in tumor resolution.^{1,4} Surgical resection of abdominal Burkitt's lymphoma was found in early studies to correlate with remission and increased survival when at least 90% of tumor could be removed¹⁰, and may play a role in treatment in health care systems where multiagent chemotherapy is unavailable, but such surgery is accessible.¹

There have been various trials looking at chemotherapeutic regimens in African Burkitt's lymphoma. After the discovery that even single doses of chemotherapy caused recovery and even remission in some children, there was interest in the efficacy of multiagent regimens. Seminal research by Dr. Charles Olweny and his team in Uganda found that, while single agent regimens with cyclophosphamide were as effective as combination regimens of cyclophosphamide, vincristine and methotrexate in inducing remissions, the patterns of relapse were quite different. Cyclophosphamide monotherapy was associated with relapse both in the central nervous system and systemically, while the combination regimen was more solely associated with central nervous system relapse.¹¹ Further research by Dr. Olweny found that CNS relapse does not necessarily portend poor prognosis, so much as disease stage.¹² This set the groundwork for researching the role of

intrathecal therapy in African Burkitt's, which found a role for intrathecal chemotherapy both as prophylaxis and treatment.¹³

More recent experiences over the past decade have looked at replicating findings from the Uganda Cancer Institute in other sites in Africa. A series of studies have been conducted by Dr. Peter Hesseling in Malawi for children with Burkitt's lymphoma. His pilot study using a 70-day regimen consisting of cyclophosphamide, vincristine, methotrexate, and cytarabine found similar event free survival rates to Dr. Olweny.¹⁴ Building off of these studies with a goal of creating shorter regimens with less cost and morbidity, his group devised a modified chemotherapy regimen modeled off of their pilot study. Although this study did include more children with progressive disease compared to their earlier trials, this study found no significant improvement in overall event free survival.¹⁵ Further research by Dr. Hesseling's group has found promise in shorter, more cost-effective regimens of oral or intravenous cyclophosphamide, combined with intrathecal methotrexate.¹⁶

The research on African children with Burkitt's lymphoma often includes children who are HIV-positive and HIV-negative. In recent years there has been an interest in determining if clinical presentation and treatment Burkitt's lymphoma differs based on HIV status. Dr. Jackson Orem's group conducted a retrospective study of clinical records at the Uganda Cancer Institute from 1994-2004, and found that while there was no difference in response to treatment with chemotherapy between the 2 groups, that children who were HIV-positive had poorer survival.¹⁷ Further research by his group found increased mortality in HIV-positive children with Burkitt's lymphoma in a 20 year retrospective study of the Uganda Cancer Institute. Interestingly, HIV-positive children with Burkitt's lymphoma had reduced mortality after the introduction of antiretroviral therapy in Uganda, though the mortality rate of HIV-positive children with Burkitt's lymphoma was still higher than that for HIV-negative children with Burkitt's lymphoma throughout the whole study period.¹⁸ Given the large burden of disease of both Burkitt's lymphoma, and HIV/AIDS in sub-Saharan Africa, HIV-associated Burkitt's lymphoma

warrants further research. Whether HIV seropositivity renders Burkitt's lymphoma to react differently to chemotherapy is a question that remains unanswered.

Challenges in treatment of Burkitt's lymphoma in African children

While pediatric oncology treatment faces many challenges in resource-rich settings such as the United States and Europe, the obstacles are staggering in resource-poor settings, which is the environment for many African children with Burkitt's lymphoma. While the cure rates for pediatric malignancies in the United States are greater than 80%, the survival rates for childhood Burkitt's lymphoma pale in comparison, despite the superb chemosensitivity of the tumor, only nearing at best 40-50%. The recent 20 year retrospective study of outcomes of childhood Burkitt's lymphoma at the Uganda Cancer Institute found that there was no clear decrease in mortality among children diagnosed more recently versus those diagnosed earlier in the study period, and that the proportion of children presenting with advanced disease stage has not decreased over time, both findings which may suggest that barriers to health care are still a significant hurdle to treatment and cure.¹⁸

The barriers to health care occur on many levels. Epidemiology studies are crucial to determine the target patient population, and these are few in number. Diagnostic options are inaccessible to many due to cost of diagnostic procedures, and lack of prompt pathologic interpretation of specimens. Difficulty accessing oncologic treatment secondary to distance and finances is a major barrier, and often results in late presentation of disease, which is a major poor prognostic factor for Burkitt's lymphoma.¹² Overseas collaborations, while offering many patients access to subsidized treatment, often come too late. The complications of illness, such as anemia and thrombocytopenia are difficult and dangerous to treat without a safe blood supply. Many children also succumb to illnesses secondary to their immunosuppressed state.¹⁹ The African public health sector has many priority areas of focus, such as tuberculosis and the HIV/AIDS epidemic, and funding for African Burkitt's lymphoma treatment programs is often unavailable. Historical disparities may also play a role, as political instability in many African

countries has destroyed and continues to destroy any healthcare infrastructure that may have been created.⁶

Despite these challenges, there have been efforts made to overcome some of the barriers to healthcare. The World Health Organization (WHO) and the International Society of Pediatric Oncology (Société Internationale d'Oncologie Pédiatrique, or SIOP) have made global cancer a priority in health care reform, and the international health community has issued many statements highlighting the crucial role of cancer abroad as a major public health concern.^{20,21} Efforts to consolidate treatment and make oral options for chemotherapy are steps in the right direction. Studies have shown that systems with established supportive care services are also linked to better outcomes.²² In addition, forming collaborative relationships, both within and outside of the African continent, would be a way consolidate resources for care that would offer benefit to more patients.²³

The treatment and cure of African pediatric cancers is crucially linked to not only effective medical treatment, but improvement of health care infrastructure. Without effective strategies to overcome barriers in health care delivery, even the most superb medical therapy is obsolete. As a global health community, we are responsible together to reduce the undeniable disparity in oncologic health care outcomes for children with cancer in the Western world and African children with Burkitt's lymphoma.

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