Modern chemotherapy for childhood Burkitt lymphoma has its origins in Africa, where treatment evolved from one or two doses of single agents, which were curative in some patients, to combinations of non-cross-resistant drugs. Subsequently, in Europe and the United States, high-dose methotrexate, high-dose cytarabine, etoposide, and ifosfamide were found to be active in children with recurrent disease and were incorporated into primary therapy for patients with high-risk disease. These third-generation protocols produce overall cure rates around 90%. Therapy regimens for adults with Burkitt lymphoma have been developed by modifying second-generation pediatric protocols, and few investigators have used the third-generation pediatric regimens that include higher doses of methotrexate and additional agents. The weight of evidence strongly suggests that high-dose therapy with stem cell rescue in first remission cannot substitute for intensive therapy from the outset. Tolerance of intensive regimens by the elderly is a legitimate concern, but it seems appropriate to modify therapy only when necessary in individual patients. The value of rituximab and granulocyte colony-stimulating factor in patients undergoing intensive therapy (particularly the elderly) is worthy of further exploration. Because childhood diffuse large-B-cell leukemia (DLBCL) responds equally well to therapy for Burkitt lymphoma, more intensive therapy and intensive support might also give better results in at least a subset of adults with advanced DLBCL—perhaps defined on the basis of limited molecular profiling, which has provided new information about the categories of aggressive B-cell lymphomas.

Introduction
For many years after its discovery in children in equatorial Africa—Burkitt’s classic paper was published in 1958 [1]—Burkitt lymphoma (BL) was thought to be a childhood lymphoma with rare cases occurring in adulthood. This is probably so in Africa, where the incidence of childhood BL is high (5 to 10 per 100,000 per year) and the peak incidence is at age 6 to 7 years, but in countries at a higher level of socioeconomic development, where childhood BL has a much lower incidence (perhaps 50-fold less), the incidence of BL in children and adults is similar. In high-income countries, BL accounts for approximately half of all non-Hodgkin’s lymphoma (NHL) in children, and, not surprisingly, treatment has evolved mainly from the early experience in Africa. In contrast, in adults, in whom BL accounts for only a small proportion of cases of NHL, BL was long included with many other “diffuse aggressive” lymphomas (usually the intermediate- and high-grade categories defined in the Working Formulation for Clinical Usage [2]) or was considered a variant of acute lymphoblastic leukemia (ALL) and treated accordingly. Even today, many adult patients with advanced disease continue to be treated with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), other so-called Adriamycin (doxorubicin)–containing regimens, or with “leukemia” regimens. Therapy designed for ALL gives poor results, and for many years BL morphology, extranodal disease (the most frequent presentation of BL), and high levels of expression of Ki-67 (a characteristic feature of BL) have been known to be poor prognostic indicators in “aggressive” adult NHL [3,4]. In fact, small noncleaved lymphomas (now classified as BL and non-BL), along with lymphoblastic lymphoma and immunoblastic lymphoma, were included in the high-grade category of the Working Formulation for Clinical Usage because of their poor survival rate at 5 years (23%) when treated with doxorubicin-containing regimens [2].

In Africa, bone marrow involvement in BL is uncommon, even after recurrent disease [5], and marrow involvement was once considered by some to be incompatible with a diagnosis of BL. However, following the development of the French-American-British (FAB) classification of ALL, it was recognized that a small percentage of ALL cases (known as L3 type) morphologically resemble BL. The expression of surface immunoglobulin by the majority of L3 cases provided further evidence that L3 ALL was, for the most part, synonymous with BL. Coupled with the recognition that cases otherwise
clinically indistinguishable from BL often had bone marrow involvement, this evidence led to many patients being treated with ALL therapy despite the very poor prognosis of L3 ALL treated in this way [6,7]. In children, the issue of whether BL should be treated as a leukemia or lymphoma was resolved by the early 1980s, with the results of a randomized study conducted by the Children's Cancer Study Group. In this study, a protocol based on ALL therapy produced a progression-free survival rate of 29% for children with extensive “undifferentiated lymphoma” (later known as small, noncleaved lymphoma before becoming, once again, BL). This was clearly inferior to the 50% rate produced by a simple combination chemotherapy protocol with repeated cycles of COMP (cyclophosphamide, vincristine, methotrexate, and prednisone). The ALL-based therapy, however, gave better results than COMP for patients with lymphoblastic lymphoma [8,9]. Continued progress in the management of pediatric BL has been made since that time in both Europe and the United States, through the development of increasingly intensive but shorter protocols. Event-free survival (EFS) rates for all patients are presently about 90% at 3 to 5 years [10–14]. These are the equivalent of cure rates because (as originally shown in Uganda) relapse occurs almost exclusively within a year from diagnosis. Even the highest-risk patients, those with bone marrow involvement or a leukemic presentation (unfortunately, often still referred to by pediatric oncologists as “acute B-cell leukemia,” although the World Health Organization [WHO] classification does not include such a category) and central nervous system (CNS) involvement, have only slightly lower EFS rates.

In view of the good results being achieved in children by the 1980s, some oncologists developed treatment protocols for adults based on the successful pediatric regimens, and reported improved results [6,7,15,16]. Others explored the use of high-dose therapy and stem cell rescue (HD-SCR) in first remission after standard NHL regimens [17]. The evaluation of case series in which only patients who receive stem cell transplants are included must take into account the likelihood of selection biases, and it is clear that low-intensity regimens such as CHOP and its immediate successors, followed by HD-SCR, cannot possibly produce the same kinds of results achieved with effective pediatric regimens in patients with extensive BL; little more than half of patients treated with CHOP or similar regimens can be expected to achieve complete remission (CR), so a high proportion would not even be eligible for HD-SCR.

The existing data, although arguably insufficient to draw a firm conclusion for older adults (who may have a worse prognosis but account for only a small proportion of BL cases), support the view that better overall results in adults would be obtained by using protocols identical to those now giving the best results in children, modified only when essential, in the presence of organ failure or comorbidities [7,10,11,18,19,20,21]. Reported results regarding tolerance of such protocols (modified or not) in adults are mixed, but at least one of these intensive protocols, CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate, alternating with ifosfamide, etoposide, and high-dose cytarabine), has been used in patients with AIDS, who were reported to tolerate it well [22]. This result suggests that most adult patients, with appropriate supportive care including granulocyte colony-stimulating factor and early administration of antibiotics for those who are neutropenic, would be able to tolerate therapy of this degree of intensity with toxicity similar to that encountered in children and less than that associated with HD-SCR. The use of such protocols could lead to overall improvements in survival rates in adults with BL, Burkitt-like lymphoma (BLL), or, potentially, some subgroups of patients with diffuse large-B-cell leukemia (DLBCL).

The purpose of this article is to briefly review the evolution of primary therapy for BL, with particular emphasis on the seminal findings in Africa several decades ago, and to highlight some of the factors that appear to have led to the markedly improved outcome in children in recent decades. The treatment of adults with BL in the context of these results in children is also addressed.

The Evolution of Treatment in Africa

Burkitt, in his early descriptions in Uganda of the tumor that now bears his name, brought attention to its remarkable propensity to involve the jaw, particularly in young children [1]. The tumor also frequently involves the abdomen—the most common site of disease in patients outside Africa and New Guinea (where jaw tumors are also very common)—and a variety of other sites, including the spinal extradural space, cranial nerves, and meninges [23]. In contrast to BL in North America and Europe, African BL rarely involves the bone marrow.

In addition to clinical differences, there are differences in the distribution of chromosomal breakpoint locations in the characteristic myc-immunoglobulin translocations, and also in the association with Epstein-Barr virus (EBV): the tumor cells contain viral genomes in only 10% to 15% of North American and European cases, compared with essentially 100% of African cases [23,24]. It will be interesting to supplement these studies by comparing the gene expression profiles of BL in African and non-African cases as well as in cases with and without EBV; insights may be obtained into the role of EBV in pathogenesis. Whether BL in different world regions or populations responds differently to therapy is not known—meaningful comparative studies of this kind are very difficult to perform—but there are enough similarities in clinical behavior and treatment response for the early studies in Africa to have provided the foundations of modern chemotherapy, at least in children.