Improving the accuracy in prognosis for Burkitt lymphoma patients

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Jorge J Castillo

Author for correspondence: Division of Hematologic Malignancies, Dana Farber Cancer Institute, M221, 450 Brookline Ave, Boston, MA 02215, USA
Tel.: +1 617 632 6285
Fax: +1 617 632 4862
jorgej_castillo@dfci.harvard.edu

Omar Nadeem

Division of Hematology and Oncology, Rhode Island Hospital, 593 Eddy St, Providence, RI 02903, USA

A recent population-based study on 2000 adult patients with Burkitt lymphoma presented a novel score that takes into account age, race and clinical stage to prognosticate survival. The outcome of patients with Burkitt lymphoma has improved in the last decade, likely due to intensive chemotherapy regimens and anti-CD20 monoclonal antibody therapy. There is, however, a lack of improvement in the outcome of patients older than 60 and in black patients. In this article, we discuss the findings of that study as well as the areas of uncertainty and/or disparity in the prognosis of patients with Burkitt lymphoma.

Burkitt lymphoma (BL) is a highly aggressive lymphoma characterized by a translocation involving the *c-MYC* oncogene located on chromosome 8. Despite its aggressive nature, reasonably high cure rates can be achieved. The treatment of patients with BL almost invariably involves intensive combination chemotherapy and central nervous system prophylaxis [1,2]. Traditionally, pediatric and adult populations have been treated rather similarly, with the former population having better outcomes, presumably due to better tolerability [3]. The addition of the anti-CD20 monoclonal antibody rituximab (Rituxan®, Genentech, South San Francisco, CA, USA) to conventional chemotherapy regimens has improved response rates in various small studies, but a benefit of this addition on the survival of BL patients has not been validated in large, randomized controlled trials [4].

The prognosis of adult patients with BL is variable, and the data on prognostic factors are rather scant. Early on (1980), a study on 42 patients with African BL concluded that markers of the burden of disease such as stage, lactate dehydrogenase and uric acid levels were the most important prognostic factors [5]. More recently, a medium-sized population-based study from Sweden (n = 156 BL patients) and a small study from Singapore (n = 40 patients) identified age, clinical stage and performance status as prognostic factors [6,7]. In the Swedish study, the 2-year overall survival (OS) of adult patients with BL ranged between 30 and 90%, depending on the number of risk factors identified. Interestingly, the addition of rituximab did not seem to improve outcomes [7]. The impact on prognosis of HIV infection and the increasing use of antiretroviral therapy is currently unknown, as this population encompasses approximately 20% of BL cases in the USA.

A recent population-based study using the Surveillance, Epidemiology, and End Results (SEER) database have further refined prognostic factors in BL [8]. The study included 2284 adult BL patients from 1998 until 2009 in whom BL was the first malignancy. It is important to note that the outcome of interest was relative survival (RS) rather than the typically used OS. RS is the ratio of the observed survival rate in a population (i.e., OS) to the expected survival rate from a similar population of cancer-free individuals [101]. Older age, black race and advanced stage were associated with significantly worse outcomes. Based on these results, a prognostic score was generated assigning 1 point for age 40–59 years or black race, 2 points for age 60–79 years or stage III/IV and 4 points for age ≥80 years. The patients were

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classified as low (0–1 points), low-intermediate (2 points), high-intermediate (3 points) and high risk (≥4 points), with 5-year RS rates of 71, 55, 41 and 29%, respectively.

The survival analysis in BL patients over the past decade only showed improvement in patients younger than 60 years of age. In the time period analysis, the 3-year RS in patients 20–39 years increased steadily during the 1990s likely due to the introduction of intensive regimens, and continued improving during the 2000s, which correlates with the introduction of rituximab. The group of patients 40–59 years also experienced an improvement during these two periods although at a lower degree than the younger cohort. However, patients >60 years did not seem to obtain benefit from intensive regimens or rituximab. One could hypothesize that to benefit from rituximab, one should first benefit from intensive regimens. These findings solidify age as the most powerful prognostic factor in BL. However, whether survival in BL is a function of age due to tolerability and/or toxicity issues, or whether older patients are more resistant to chemoimmunotherapy needs to be further investigated.

Not surprisingly, clinical stage appeared to be the second most important prognostic factor. However, the staging system used by SEER (i.e., Ann Arbor), although a commonly used system and reliable reflection of the burden of disease, may not be ideal in BL, as it does not accurately portray the extent of extranodal involvement. For this reason, other staging systems such as the St. Jude/Murphy are used mainly in pediatric populations. However, such staging systems were developed when surgery was routinely used for diagnostic and therapeutic purposes. Due to the advent of highly effective chemotherapy, surgery is no longer considered a standard of care for BL. It is likely, however, that other markers of burden of disease such as lactate dehydrogenase levels or bone marrow involvement could also be of value for survival prognosis in patients with BL.

A novel finding was the significantly worse outcomes in blacks compared with other races. The etiology of this is unclear as the trend was independent of socioeconomic status, although access to care data was not available. A higher proportion of black patients do present with stage IV disease but the outcomes are inferior regardless of stage. Interestingly, the period analysis showed a lack of benefit in blacks seen during the 2000s (rituximab era). Few studies have suggested that black patients are less likely to receive chemotherapy or rituximab as part of their therapy [9]. However, it is unclear whether the source of the disparity is a lack of healthcare access, refusal of therapy or a distinct metabolism of chemoimmunotherapy in such demographic. Another population-based study using the SEER database that included pediatric patients also confirms our findings of poor outcomes in black patients with BL [10]. Furthermore, other epidemiological studies have associated blacks with worse outcomes in diffuse large B cell and Hodgkin lymphoma [11,12]. Certainly, additional research should be performed to address these disparities.

BL remains a potentially curable disease and cure should be the goal of our therapy, whenever possible. Based on recent studies, the prognosis of patients with BL has improved with the advent of intensive chemotherapy and rituximab. The prognostic tool described above has several potential applications. First, it provides meaningful information that practitioners can include in their clinical discussions with patients and families. Second, it could be used in the design of prospective clinical trials to uniform interpretation. Finally, specific groups of patients who might not benefit from our current strategies have been identified (i.e., patients older than 60 and blacks). In such cases, moving away from toxic and potentially useless regimens might be the more humane pathway but, overall, it provides a platform to focus our research efforts on improving therapies for these patients. One approach would be intensifying therapy with the introduction of high-dose chemotherapy followed by autologous stem cell transplant. A recent study has shown improvement in survival in patients with high-risk diffuse large B-cell lymphoma who underwent autologous stem cell transplant [13]. However, tolerability could be an issue and this approach would be reserved for patients with excellent performance status. A second approach would be to move away from standard chemotherapy and use new generation drugs such as monoclonal antibodies, antibody–drug conjugates or B-cell receptor modulators such as Bruton tyrosine kinase or phosphatidylinositol-3-kinase inhibitors. For instance, blinatumomab, a bi-specific T-cell engager monoclonal antibody, is a novel molecule with two variable regions, one specific for CD3 and one targeting CD19; hence, allowing effectors T cells to come into direct contact with malignant B cells [14]. Blinatumomab has shown to be of benefit in patients with relapsed B-cell acute lymphoblastic leukemia, a disease equally aggressive as BL [15]. The careful design and execution of prospective multi-institutional studies focusing on BL patients less likely to benefit from standard regimens are needed.

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