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Outcomes of patients with Burkitt lymphoma older than age 40 treated with intensive chemotherapeutic regimens

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Abstract

Burkitt lymphoma is a highly curable disorder when treated with modern intensive chemotherapy regimens. The majority of adult patients with Burkitt lymphoma in the United States are over age 40. Older patients have historically been underrepresented in published clinical trials of modern intensive therapy, and the outcome of these patients has not been systematically reported. We therefore obtained and analyzed primary data from 14 Burkitt lymphoma treatment series and confirmed that older patients (age > 40) are underrepresented in the literature. Historically inferior outcomes of this age subgroup have improved substantially over time. We conclude that 1) modern intensive chemotherapy regimens should remain the standard of care for patients > age 40 with Burkitt lymphoma, 2) selected patients > age 40 now have highly favorable outcomes, and 3) future studies should include formal analysis of this subgroup of patients.

Keywords

Burkitt lymphoma; adult; elderly; outcome; chemotherapy

Introduction

Burkitt Lymphoma is an uncommon form of non-Hodgkin lymphoma (NHL) in adults, with an incidence of approximately 1200 patients per year in the United States[1]. Current standard therapy for Burkitt lymphoma in children consists of short duration, dose-intensive, multi-

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agent chemotherapy with CNS prophylaxis. With these treatments, most pediatric patients are cured of their disease, with long term survival of 60-90% [2-4]. When evaluated in "adults", defined as age > 15 or 18 in most series, these regimens have resulted in outcomes comparable to the pediatric experience[5] and are the standard therapy for adult patients.

However, the adult population of patients with Burkitt lymphoma is a heterogeneous group, including a substantial proportion of older patients. We reviewed the SEER database (2007) and determined that "older" adults (age > 40) account for 59% of incident Burkitt lymphoma cases. In other lymphoid malignancies, including Acute Lymphocytic Leukemia (ALL), older patients have inferior outcomes compared to younger patients due to intrinsic disease resistance, and inability to tolerate intensive therapy [6, 7].

Practice guidelines suggest that older patients with Burkitt lymphoma should be treated with similar intensive regimens as recommended for younger patients [8]. However, most of the adult Burkitt lymphoma published literature is comprised of small series that do not include subgroup analysis of older adult outcomes. To further complicate interpretation, there is no consensus definition of the "older patient". We chose to analyze patients over the age of 40 with Burkitt lymphoma since they constitute the majority of adult patients in the United States. We hypothesize that, even with a conservative definition of age>40, older patients are historically underrepresented in the published outcomes of older patients with Burkitt lymphoma, and represent a subgroup with outcomes inferior to the results published from overall study populations. In this pooled evaluation of previously unpublished adult Burkitt lymphoma treatment data, we determined the proportion of older patients in the published literature, and evaluated in the outcomes of this subgroup of patients in the modern era.

Patients and Methods

We first conducted a systematic review of published literature describing the outcome of adult patients (defined in this study as age >15 years) with confirmed de novo Burkitt lymphoma (REAL/WHO defined)[9], from series published between January 1989 and September 2007. The following databases were searched: PubMed, Web of Science, and Cochrane Library. Search terms included: Burkitt lymphoma, small non-cleaved cell lymphoma, highly aggressive lymphoma, L3 ALL, and Burkitt leukemia. References cited in candidate articles were manually searched. Inclusion criteria for the present study were as follows: newly diagnosed, HIV negative, Burkitt lymphoma with confirmed histology including at least 10 patients in the series.

Corresponding authors of eligible manuscripts then were approached to provide further data from each series detailing the number of patients over the age of 40 and their overall survival (OS) at 2 years for inclusion in a pooled database, resulting in this international collaborative effort. To maximize participation, we limited the data requested of the corresponding authors to simply the number of patients over 40 in their respective series and an aggregate estimate of 2 year OS of this older adult subgroup.

The median age at diagnosis and the proportion of cases diagnosed in patients > age of 40 in the United States was calculated using the Surveillance, Epidemiology and End Results (SEER) limited-use data (1973-2004 version) and the National Cancer Institute Surveillance Research Program SEER*Stat software version 6.3.6 (www.seer.cancer.gov/seerstat). Estimates were based on all cases diagnosed in the SEER 9 registry regions, ICD-O-3 histological types 9687 and 9826, from 2001-2004. SAS statistical software (SAS Institute, Cary N.C.) was used for median estimation and frequency table generation.

Results

Twenty manuscripts were identified that met our inclusion criteria. Only 5 contained quantitative data regarding older adult patient enrollment and subgroup analysis of outcome. These manuscripts were inconsistent in their definition of the “older” adult patient cohort. Thirteen investigators provided adequate data for inclusion detailing the number of patients from their treatment series older than age 40, and their outcome [5, 10-21] (Table 1). Three of the included manuscripts are reports of retrospective analyses[12, 16, 21]; the remaining 10 are the result of prospective study design. One manuscript contained two series of patients, which are reported separately in our database [13]. Further detail on the patient population, treatment specifics, and patient outcomes for each trial has been included in numerous other reviews[22, 23], and is outside the scope of this brief report.

A total 543 patients were included in these 13 manuscripts, and 229 (42.2%) were over the age of 40. The number of patients over the age of 40 included in studies published prior to 2000 was 29.5% of total patients enrolled (see Figure 1A). In contrast, for studies published in 2000 or after, 53.7% of patients were over the age of 40.

The subgroup of patients over the age of 40 had inferior median OS as compared to the OS for all patients enrolled in 10 of the 14 series of patients evaluated (Figure 1B). In studies published prior to 2000, only 3 of 7 studies demonstrated the “older patient” cohort 2 year median survival to be over 40%. In contrast, for studies published in or after 2000, only one had an older patient cohort 2 year median survival less than 60%.

Analysis of the SEER database (2007) revealed that “older” adults (age > 40) account for 59% of the incident Burkitt lymphoma cases (ICD-O-3 histological types 9687, 9826), and the median age at diagnosis is 45 years.

Discussion

Our study confirms that, even with our conservative definition (age>40),“older” patients with Burkitt lymphoma have historically been significantly underrepresented in clinical literature and their outcomes have never been previously systematically reported. Many of the older trials included very small numbers of older patients, limiting the ability to extrapolate published results to the majority of patients seen in the clinic. Recently, there appears to be a substantial increase the number of older patients included in clinical trials, potentially due in part to the temporal changes in trial inclusion and exclusion criteria that would allow for better representation of older patients. Our current pooled analysis represents the only substantial report of outcome of the older patient group subgroup, even within these more recent clinical trials.

From our review, older patients treated with appropriate intensive chemotherapy have historically had inferior outcomes that have significantly improved over the last seven years. This progress is likely reflective of several factors, including increasing familiarity with complicated treatment regimens, advances in supportive care, and refined diagnostic criteria of Burkitt lymphoma. While it is possible that this observed improvement among older adults is reflective of temporal changes in eligibility criteria, protocol-mandated therapy, dose intensity of therapy, and/or the number of patients in each series able to complete therapy, our results suggest that with modern diagnostic criteria, older patients do not appear to have a more treatment-resistant form of the disease, unlike the situation with ALL. Moreover, although rituximab has dramatically improved outcome in NHL[24], only one recent study in our database incorporated this therapy[20]. Ongoing international trials of Burkitt lymphoma therapy are incorporating rituximab to confirm these results.

We have concluded that older adults with Burkitt lymphoma have been historically underrepresented based on a comparison of the proportion of patients over the age of 40 in the reviewed published series to the 'expected' proportion, as determined by the age distribution of the Burkitt cases in the SEER registry during the 2001-2004 time period. While the SEER registry is valuable resource for United States cancer incidence estimates, it is important to appreciate that the lack of standardization of medical records and pathology reports from which the SEER data are collected may limit this comparison[25,26]. The Burkitt cases in the SEER database likely represent a more heterogeneous histologic group than the patients represented in the series reviewed in this report. Furthermore, the series that have been reviewed in this report include patients treated in the United States and internationally between 1977 and 2005, and the overall age distribution for Burkitt lymphoma cases could potentially limit the comparison of the over 40 subgroup representation to the contemporary SEER registry data.

Our study was not designed to compare efficacy of the various treatment regimens. Indeed, all regimens included were dose-intensive regimens that adhere to modern principles of Burkitt lymphoma therapy. The ability to compare these studies is limited by historical variations in the definition and diagnosis of Burkitt lymphoma, and heterogeneous patient populations. In addition, our retrospective approach required collection of additional information from the corresponding authors of the 20 eligible published studies, and although the majority of authors agreed to participate, some potentially applicable case series were not included. Our conclusions assume no systematic differences between the studies that were included in this manuscript and those that were not, another limitation of an analysis of historical data. Given the fact our collaboration is international, and includes over 500 patients (the largest published series of adult patients with Burkitt lymphoma) we feel this is truly representative of the available data.

In our study, we defined the "older" adult patients as age > 40. According to SEER data, patients > 60 represent approximately 30% of Burkitt lymphoma cases annually[1]. While our available data did not allow us to do so in the present study, this may be another meaningful group of patients to evaluate separately as the incidence of patient co-morbidities significantly increases, and tolerance of intensive regimens decreases, after age 60. A recent British effort to refine diagnostic criteria differentiating Burkitt lymphoma from other aggressive lymphomas determined the median age of Burkitt lymphoma to be 37 years; the few elderly patients (> 65) enrolled had significantly inferior outcome[27].

Conclusions

Few trials in Burkitt lymphoma have included substantial numbers of elderly patients. We strongly advocate for specific clinical trials of intensive chemotherapeutic regimens enrolling larger numbers of older patients in the modern diagnostic era to confirm our results, and further prospectively investigate the factors associated with differential outcomes in the older adult subgroup. However, until such prospective clinical trials are designed and completed, our results from analysis of over 200 patients over the age of 40 affirm the current Burkitt lymphoma treatment guideline recommendations of intensive therapeutic regimens for older patients, and suggest that the outcome of selected older patients treated with these regimens is quite favorable.

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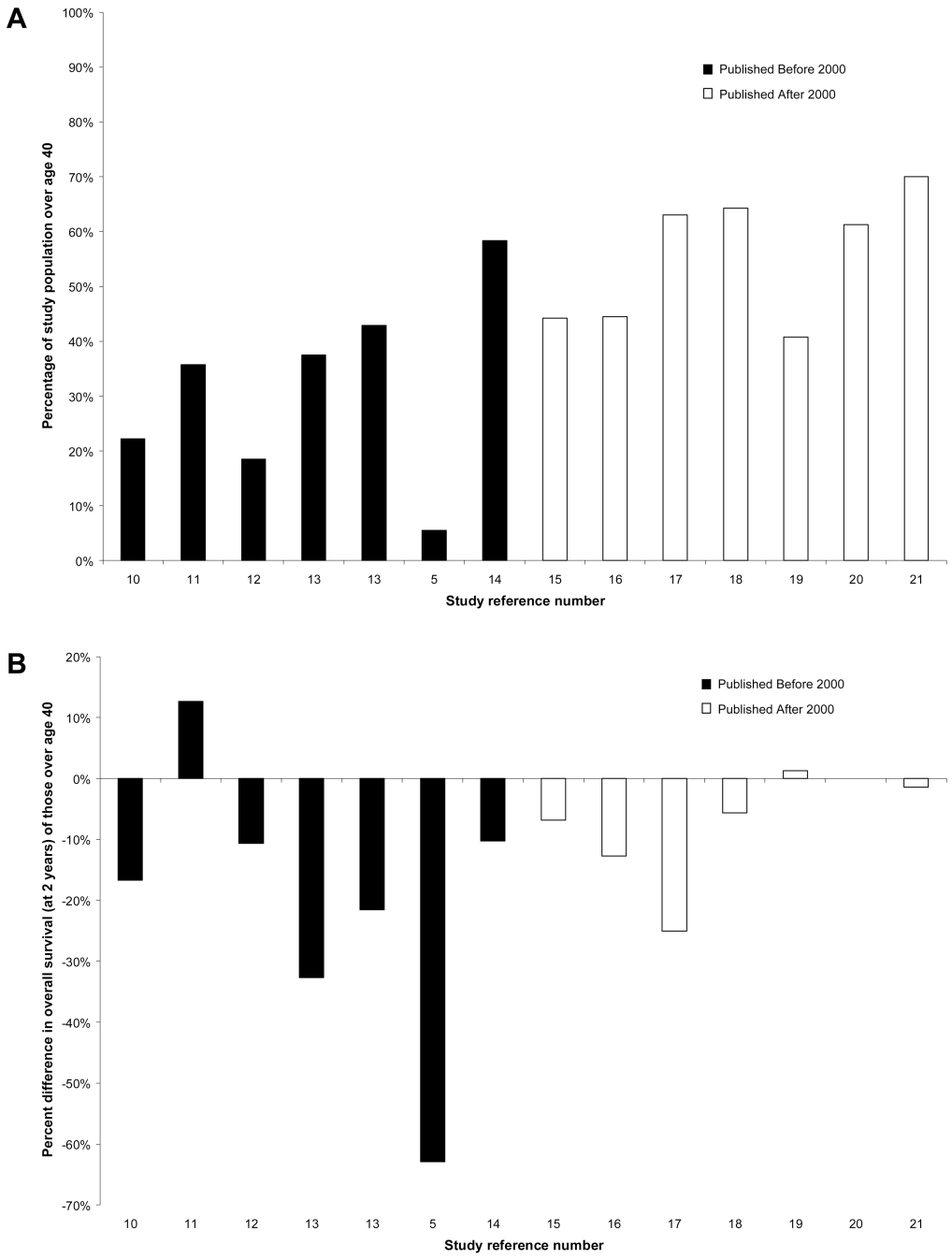

Figure 1. Representation and relative overall survival (at 2 years) of patients over age 40 in 13 reviewed treatment series

(A) Percentage of each total study population that was over age 40. (B) Percent difference in overall survival (at 2 years) for those over age 40 as compared to overall survival for the entire population, by study. For both A and B panels, treatment series are listed in chronologic order, labeled by study reference number, and grouped by year of publication (before 2000, black; after 2000, white).

Table 1

Overview of included studies

Series, year of publication	Treatment Period	Treatment Regimen	Total N	Median Age	Age Range	Overall Survival	Subjects older than 40 years		
							N	% of Total N	Overall Survival
Fenaux, 1989[10]	5/81 - 12/87	ALL-like regimen; 4 pts with SCT	18	26	16-66	30.0%	4	22%	25.0%
Pees, 1992[11]	1982-1990	Short duration/dose intensive; pediatric NHL based	14	39	16-65	71.0%	5	36%	80.0%
Soussain, 1995[12]	9/84 - 8/91	ALL-like regimen	65	26	17-65	75.0%	12	18%	67.0%
Hoelzer, 1996[13] B-NHL83	7/83 - 6/89	Short duration/dose intensive; pediatric NHL based	24	33	15-58	49.0%	9	38%	33.0%
Hoelzer, 1996[13] B-NHL86	7/89 - 1/93	Short duration/dose intensive; pediatric NHL based	35	36	18-65	51.0%	15	43%	40.0%
Magrath, 1996[5]	10/77 - 12/93	CODOX-M/IVAC	54	N/A	N/A	89.0%	3	6%	33.0%
Thomas, 1999[14]	9/92 - 6/97	Hyper CVAD	48	58	17-79	39.0%	28	58%	35.0%
Mead, 2002[15]	10/95 - 5/99	CODOX-M/IVAC	52	27	15-52	70.0%	23	44%	65.2%
Smeland, 2004[16]	1982-2001	Short duration/dose intensive; ASCT	36	N/A	15-69	regimen 2: 71%; regimen 3: 65%	16	44%	62.0%
Rizzieri, 2004[17]	5/92 - 2/00	Short duration/dose intensive	92	47	17-78	cohort 1: 54%; cohort 2: 50%	58	63%	39.0%
Lacasce, 2004[18]		Modified CODOX-M-IVAC regimen	14	47	18-65	71.0%	9	64%	67.0%
van Imhoff, 2005[19]	12/94 - 2/03	Short duration/dose intensive; ASCT	27	36	15-64	81.0%	11	41%	82.0%
Thomas, 2006[20]	2/00 - 1/05	Hyper CVAD + Rituximab	31	46	17-77	89.0%	19	61%	89.0%
Kujawski, 2007[21]	1/95 - 8/02	Short duration/dose intensive	10	51	35-71	72.0%	7	70%	71.0%