



CALGB1002 Protocol in the Treatment of Adult Burkitt Lymphoma, Outcome, and Toxicity A Single-Center Experience

Mohammad Ma'koseh, Baha' Sharaf, Khalid Halahleh, Alaa Abufara, Rula Amarin

King Hussein Cancer Center, Amman , Jordan



INTRODUCTION

◦Burkitt Lymphoma [BL] is highly aggressive B cell non-hodgkin lymphoma [NHL] characterized by high proliferation rate [Ki 67 around 100%] and deregulation of MYC gene. It is more common in pediatric age group, peaking around the age of 10 years, while in adults, it accounts only for about 1% of all NHL.

◦Clinically, it often presents with rapidly enlarging masses and involvement of extranodal sites, especially the bone marrow and the central nervous system [CNS]. Because of its rapid growth, early diagnosis and prompt initiation of treatment is important.

◦Treatment of BL in adults is challenging because of lack of randomized trials to define the best initial regimen. Most of the first line regimens are adopted from intensive pediatric protocols and include a combination of anthracycline, alkylator, vincristine, etoposide and agents to treat and prevent CNS disease.

◦Cancer and Leukemia Group B [CALGB] developed an intensive regimen [CALGB 9251] that initially included multi-agent chemotherapy with prophylactic cranial radiotherapy and 12 intrathecal chemotherapy [ITC].As 61% of patients developed severe neurological toxicity in the first cohort, in the second cohort of patients, prophylactic cranial radiotherapy was given only to patients with bone marrow involvement and only 7 ITC doses were administered. The 5-year overall survival [OS] was 52%. In a follow-up study [CALGB 1002], addition of Rituximab resulted in improvement of 4-year event free survival [EFS] and OS to 78% and 74% respectively.

◦CALGB1002 protocol was used for treatment of most BL cases in our center. The aim of our study is to describe characteristics and outcomes of adult BL patient treated with CALGB 1002 protocol.

Background

Treatment of adult Burkitt lymphoma with pediatric inspired chemotherapy protocols usually results in high cure rates with significant toxicity. Here, we report our experience with Cancer and Leukemia Group B1002 protocol.

Objective

CALGB1002 protocol was used for treatment of most BL cases in our center. The aim of our study is to describe characteristics and outcomes of adult BL patient treated with CALGB 1002 protocol

Patients & Methods

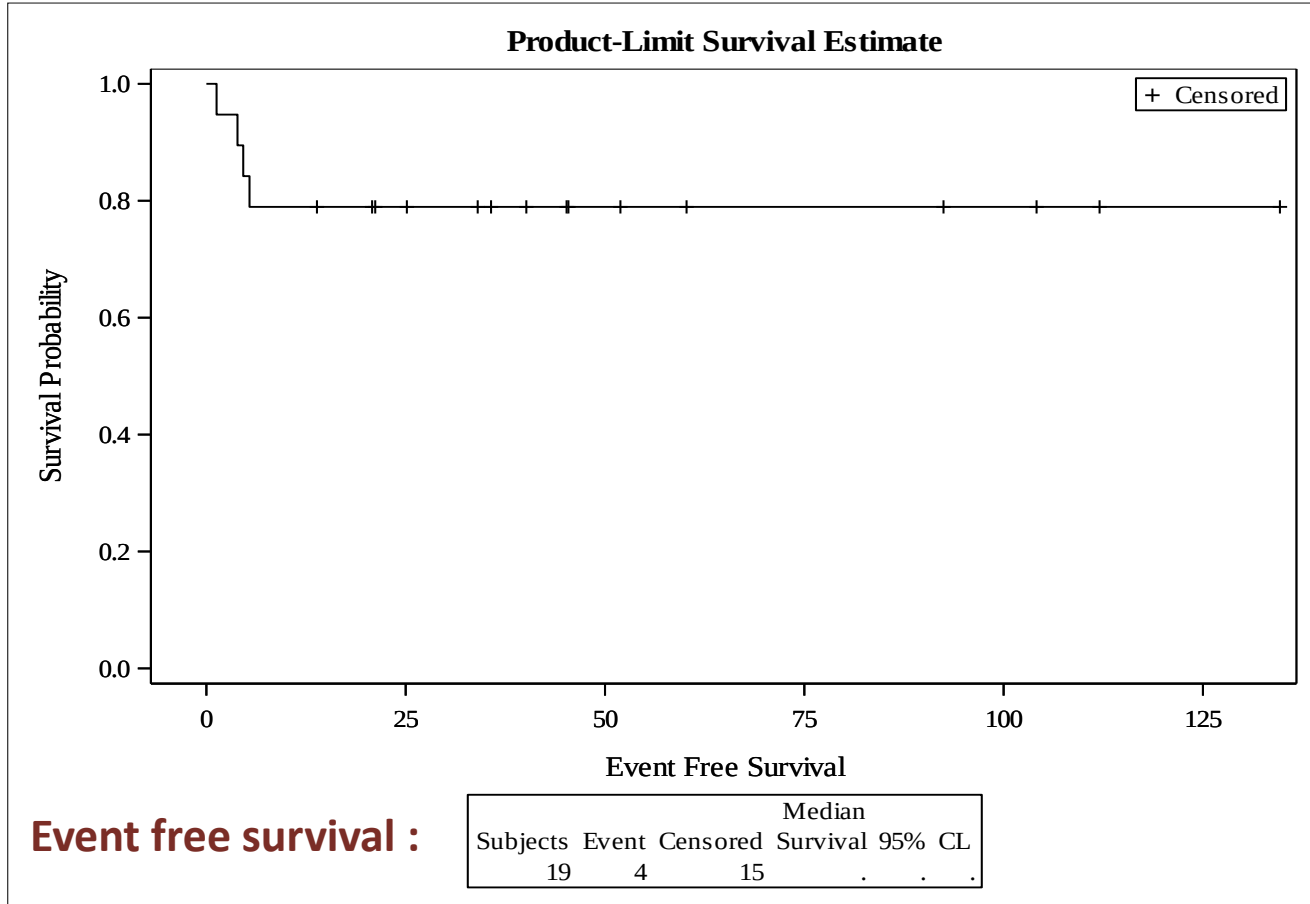
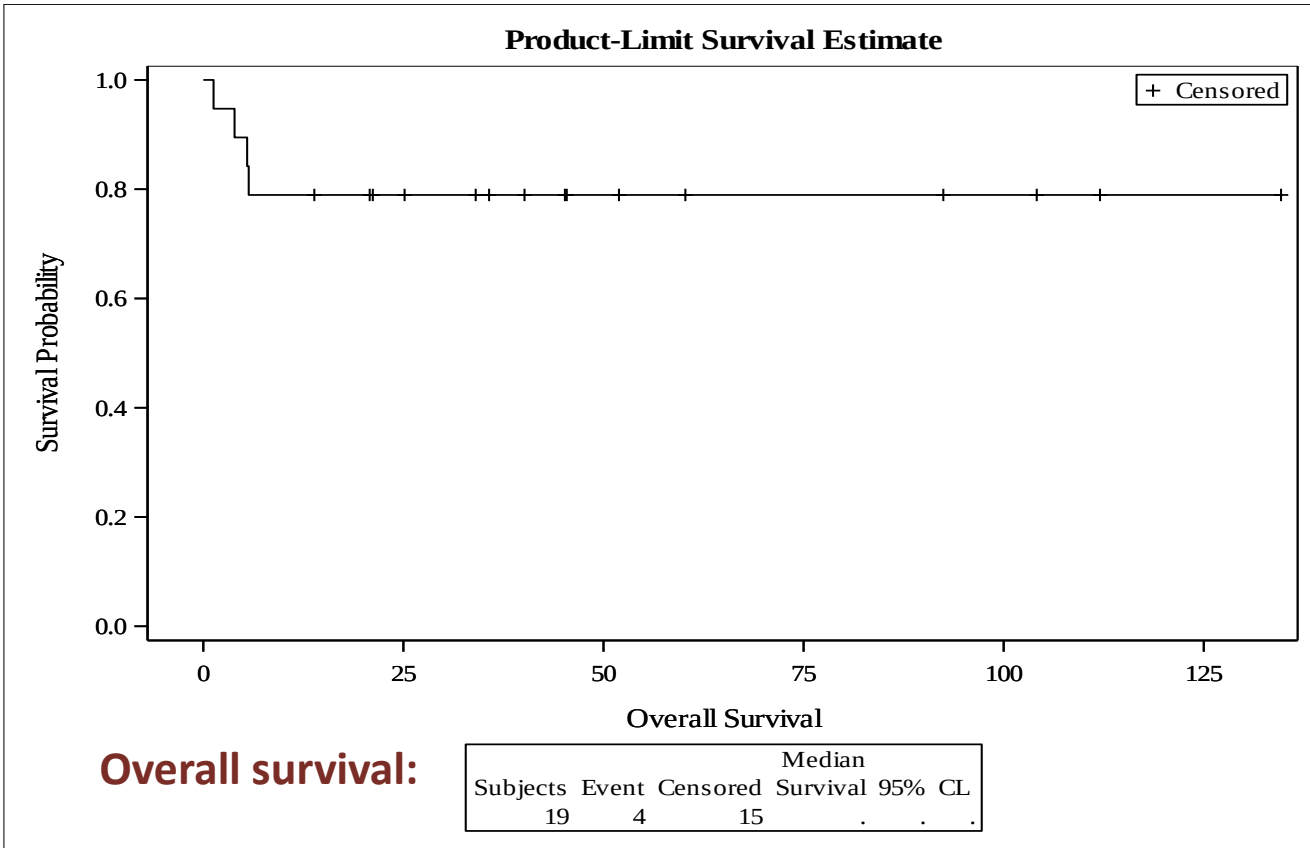
Files of adult patients diagnosed with Burkitt lymphoma and treated with CALGB1002 protocol in King Hussein Cancer Center between 2008 and 2017 were reviewed.

19 patients were included, 12 (63%) were males. The median age was 33 years (range: 19-65). 11 patients (58%) had advanced-stage disease, 14 (73.6%) had extra-nodal involvement. CNS involvement was found in 2 patients (10.5%), and bone marrow involvement was found in 2 patients (10.5%). and 13 patients [68%] had a high risk disease

. Correlation between different clinical and laboratory variables with event free survival [EFS] and overall survival [OS] by univariate and multivariate analysis utilizing the backward stepwise Cox-regression model. EFS and OS were blotted using Kaplan Meir curves.

patients' characteristics:

Variable n=(19)	Number [%]
Age	Median is 33 (19-65)
Age >60	1 (5.3%)
Male	12 (63%)
Stage	
I-II	8 (42.1%)
III-IV	11(58%)
ECOG performance status	
0-1	15 (78.9%)
2 or more	4 (21.1%)
High LDH	10 (52.6%)
Extranodal involvement	14 (73.6%)
Number of extranodal sites	
1	7 (36.8%)
>1	7 (36.8%)
Bone marrow involvement	2(10.5%)
CNS involvement	2(10.5%)
Bulky disease	5 (26.3%)
B symptoms	5 (26.3%)
Risk classification	
Low risk	6 (31.5%)
High risk	13 (68.5%)
International prognostic index	
Low (0-1)	9 (47.3%)
Low-intermediate (2)	4 (21.1%)
High –intermediate (3)	3 (15.8%)
High (4-5)	3 (15.8%)



RESULTS

◦Median time to starting treatment was 11 days [range: 8-56 days]. Total of 106 cycles were given, median time

between them was 23 days [range: 19-84 days]. All patients were given rituximab. A median of 6 doses of ITC were

given [range: 2-6]. 3 patients [15.8%] were given cranio-spinal radiotherapy. Sixteen patients [84%] achieved complete

response [CR] while the other three patients failed to achieve CR [one had a partial response, one died because of

chemotherapy related sepsis before having a response evaluation and one developed disease progression].

◦After median follow-up of 36 months, both 3-year EFS and OS rates were 78.9%. Four patients [21.1%] died; two

because of disease progression and the other two because of chemotherapy related complications. When patients were

stratified according to the IPI, there was significant difference in 3-year OS rates between patients with low IPI vs.

intermediate or high IPI [100% vs 60%, p=0.038]. On the other hand, 3-year OS rates were not significantly different

between patients with low risk and high disease [100% vs 69%, p= 0.147]

◦Univariate analysis showed that abnormal LDH, intermediate or high IPI and bulky disease correlated with worse OS.

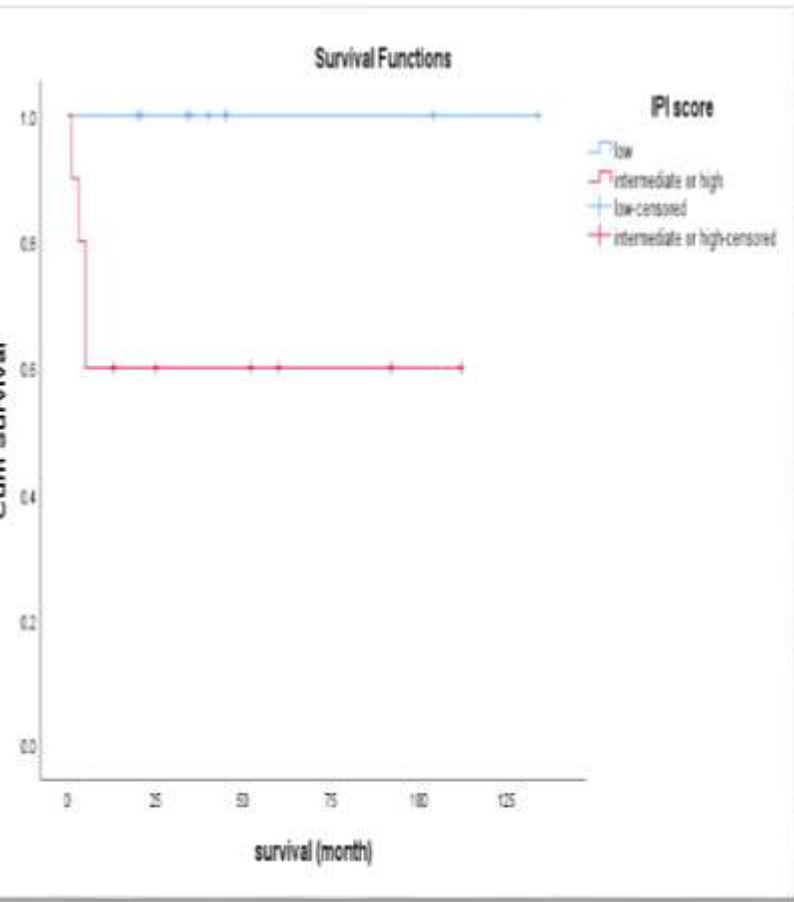
However, none of these factors was significant on multivariate analysis.

◦Hematological toxicities including grade III-IV neutropenia and thrombocytopenia were both found in 88% of patients respectively and febrile neutropenia in 89% of patients. The most important grade III-IV non-hematological toxicities were mucositis in 13 patients [72%].

Two patients [10.5%] died because of chemotherapy related toxicities, one after the second cycle and the second after the fifth cycle.

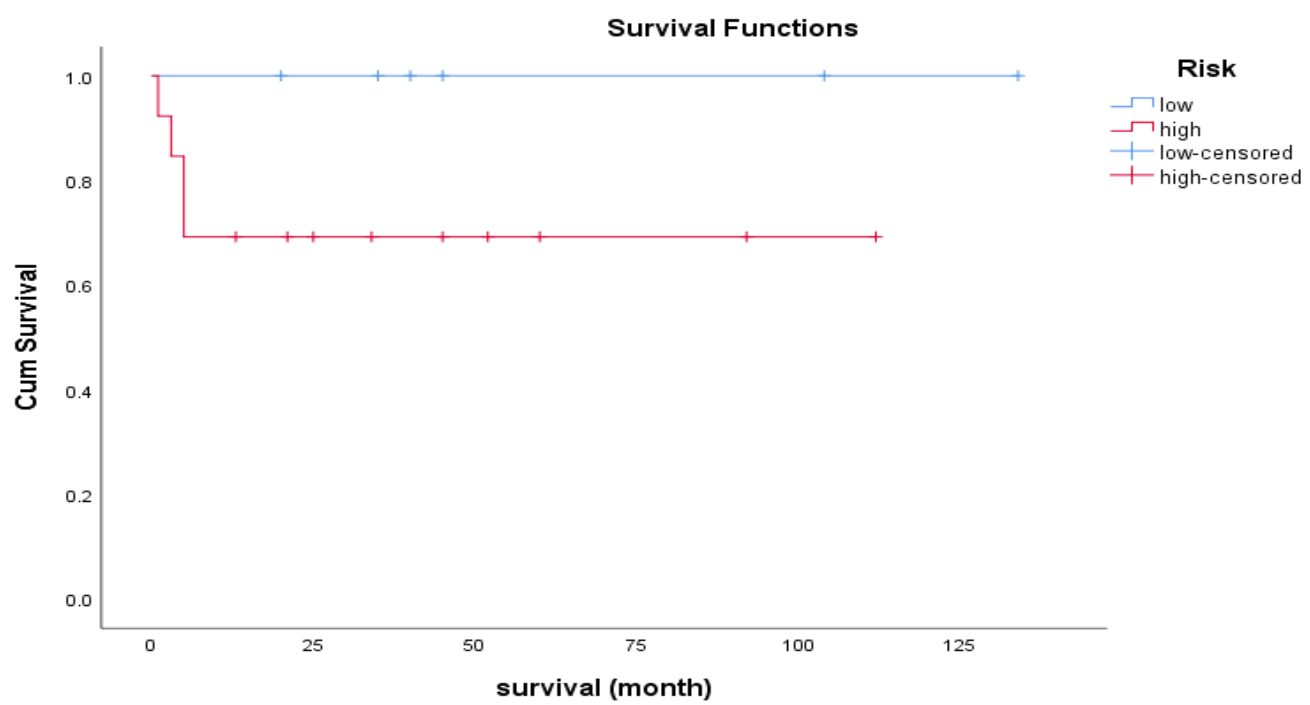
reported adverse events after each cycle							
adverse event	first cycle	second cycle*	third cycle	fourth cycle	fifth cycle	sixth cycle**	post any cycle
grade III-IV neutropenia	16(84%)	9(50%)	12(66%)	7(38%)	11(61%)	8(50%)	16(88%)
grade III-IV thrombocytopenia	15(78%)	5(27%)	13(72%)	4(22%)	12(66%)	7(43%)	16(88%)
elevated liver enzymes	9(47%)	9(50%)	7(38%)	8(44%)	9(50%)	8(50%)	14(77%)
elevated bilirubin	3(15%)	2(11%)	3(16%)	2(11%)	4(22%)	2(12%)	6(33%)
kidney impairment	1(5%)	3(16%)	2(11%)	3(16%)	4(22%)	3(18%)	11(61%)
grade III-IV mucositis	9(47%)	11(61%)	9(50%)	7(38%)	8(44%)	7(43%)	13(72%)
Febrile neutropenia	15 (78%)	9 (47%)	10 (55.5%)	6(33%)	10(55.5%)	6 (35%)	17 (89%)

Overall survival according to international prognostic index (IPI)



Univariate and multivariate analysis		Univariate analysis		Multivariate analysis	
Variable		P value	OR	P value	
Age on diagnosis > 60		0.62			
Ann Arbor stage III-IV		0.06			
Serum LDH level >1x normal		0.04	70.66	0.97	
>1 extranodal site		0.55			
bone marrow involvement		0.68			
CNS involvement		0.68			
International Prognostic Index		0.04	70.66	0.97	
B symptoms		0.30			
Bulky disease		0.01	11.37	0.49	

Overall survival in low and high risk patients, p=0.138.



Conclusion

Although CALGB 1002 protocol can be timely administered to most adult Burkitt lymphoma patients, it is associated with significant toxicity. A risk-adapted approach and consideration of other, less toxic chemotherapeutic regimens should be considered, especially in the older age group.

References

- Dunleavy K. Approach to the diagnosis and treatment of adult Burkitt's lymphoma. Journal of oncology practice. 2018 Nov;14[11]:665-71.
- Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood. 2006 Jan 1;107[1]:265-76.
- Kalisz K, Alessandrino F, Beck R, Smith D, Kikano E, Ramaiya NH , et al. An update on Burkitt lymphoma: a review of pathogenesis and multimodality imaging assessment of disease presentation, treatment response, and recurrence. Insights into imaging. 2019 Dec 1;10[1]:56.
- Kasamon YL, Swinnen LJ. Treatment advances in adult Burkitt lymphoma and leukemia. Current opinion in oncology. 2004 Sep 1;16[5]:429-35.
- Jacobson C, LaCasce A. How I treat Burkitt lymphoma in adults. Blood. 2014 Nov 6;124[19]:2913-20.
- Rizzieri DA, Johnson JL, Niedzwiecki D, Lee EJ, Vardiman JW, Powell BL, Barcos M, et al. Intensive chemotherapy with and without cranial radiation for Burkitt leukemia and lymphoma: final results of Cancer and Leukemia Group B Study 9251. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2004 Apr 1;100[7]:1438-48.
- Rizzieri DA, Johnson JL, Byrd JC, Lozanski G, Blum KA, Powell BL, et al. Improved efficacy using rituximab and brief duration, high intensity chemotherapy with filgrastim support for Burkitt or aggressive lymphomas: cancer and Leukemia Group B study 10 002. British journal of haematology. 2014 Apr;165[1]:102-11.

For further information or questions,please send an email to: maakoseh727@gmail.com