Original Study

Improving Survival of Patients With Hodgkin Lymphoma Over 4 Decades: Experience of the British National Lymphoma Investigation (BNLI) With 6834 Patients

Amy Kwan,[1] Nick Chadwick,[2] Barry Hancock[1]

Abstract

Survival for Hodgkin lymphoma has improved over the last 4 decades thanks to reducing the risks of death from primary disease and, expectantly, treatment-related toxicity.

Background: The management of Hodgkin lymphoma (HL) has changed markedly over the last 50 years. This is due to the expanding understanding about the biology of the disease, the development of increasingly efficacious multimodal treatment, and the recognition of how to reduce late effects. The British National Lymphoma Investigation (BNLI) was formed in the 1970s to coordinate UK research in the diagnosis and treatment of lymphoma. We describe the improvement in trial patient survival over 4 decades. **Patients and Methods:** This analysis is of data on 6834 patients with a de novo diagnosis of HL registered onto studies with BNLI oversight from January 1, 1970, to December 31, 2009. Patients were subdivided in 4 groups according to their decade of registration; 1970s, 1980s, 1990s, and 2000s. Because of the lengthy data collection period, there is a difference in duration of follow-up between decade groups, with median follow-up in the 1970s group of 28.2 years, 18.0 years in the 1980s group, 9.4 years in the 1990s group, and 5.4 years in the 2000s group. Comparison between data in all 4 groups is not possible beyond 13.4 years (maximum duration of follow-up in the 2000s group), and so a cutoff has been applied at 14 years. Data on overall survival, cause of death, primary treatment modality, and incidence of secondary malignancy were collected. **Results:** Clear and statistically significant improvements in survival curves between the decades were present, with 10-year overall survival increasing from 62.4% in the 1970s to 89.6% in the 2000s. There was a suggestion that second malignancy and cardiac-related deaths have been reducing over time, but longer follow-up is needed for the later decades to confirm this trend. **Conclusion:** Results support existing registry data demonstrating that survival for HL has improved over the 4 decades analyzed. This data set is robust and validated, and it adds valuable understanding to the reasons behind the survival curves, which are a balance between efficacious therapies and decreased death related to cardiac conditions and second malignancies.

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Introduction

Over the past 50 years, survival in patients diagnosed with all stages of Hodgkin lymphoma (HL) has improved dramatically. The driver for improvement has been the strong research ethos of hematologists and oncologists, which has led to considerable progress in optimizing the treatment of this unique disorder. Understanding of the biology of the disease, development of novel chemotherapy regimens, and advancement in radiotherapy techniques have not only given patients with advanced disease the probability of cure but has also been a platform for the development of chemotherapy and radiotherapy regimens in a number of other malignancies.

The British National Lymphoma Investigation (BNLI) was formed in 1970 to coordinate medical research into the diagnosis and treatment of lymphomas. Since then, data on nearly 20,000 patients have been collected and several major clinical trials organized, the results of which have influenced treatment worldwide.

[1]Academic Unit of Clinical Oncology, University of Sheffield, Weston Park Hospital, Sheffield, UK
[2]Cancer Research UK and UCL Cancer Trials Centre, London, UK

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Address for correspondence: Barry Hancock, MD, Weston Park Hospital, Whitham Road, Sheffield S10 2SJ, UK
E-mail contact: b.w.hancock@sheffield.ac.uk

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The BNLI was initially a loose confederation of clinicians and pathologists who came together to further the investigation and management of patients with Hodgkin, and later, non-HL, in general hemato-oncology practice. From its inception, the BNLI had 2 central innovative concepts. First was the necessity for central histologic review with accurate diagnosis and histologic classification, and second was the value of randomized multicenter controlled trials. Histologic review was provided by the pathology service based at Mount Vernon Hospital and data management by the BNLI data center at the Middlesex Hospital Medical School. These central principles have provided a major data resource for lymphoma investigation spanning several decades and have been instrumental in identifying best practices for patient management as well as profiling the clinicopathologic characteristics of the disease.

During the 1980s and 1990s, various UK lymphoma groups began to work more closely together, initially through the United Kingdom Lymphoma Group and then through the United Kingdom Co-ordinating Committee for Cancer Research lymphoma group. This process of greater cooperation ultimately led to the creation of the National Cancer Research Institute Lymphoma Clinical Studies Group in 2002. The BNLI was actively involved in this process of greater cooperation and in 1997 became part of the Cancer Research UK–funded Cancer Trials Centre at University College London. Funding for the BNLI came primarily from the Lymphoma Research Trust initially, but subsequently funding was also provided by Cancer Research UK.

Since its formation, the BNLI has been involved in a number of key internationally important trials[1] (Table 1) that have confirmed that prednisolone is an integral part of the MOPP (mechlorethamine, vincristine, procarbazine, prednisolone) regimen[2] and have demonstrated that the use of MOPP substitutes (eg, LOPP [chlorambucil, vincristine, procarbazine, prednisolone]) are effective and may be less toxic.[3] The BNLI has also been involved in developing and evaluating a number of alternating and hybrid regimens, which can be administered safely and with good efficacy. These include a MOPP regimen substitute (chlorambucil, vinblastine, procarbazine, prednisolone [ChIVPP] or LOPP) administered in an alternation with the ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) substitutes PABIOE (prednisolone, doxorubicin, bleomycin, vincristine, etoposide) or EVAP (etoposide, vinblastine, doxorubicin, prednisolone).[4-6] In addition, the phase 3 trial of the Stanford V regimen with appropriate radiotherapy, compared to ABVD, demonstrated equivalence in terms of disease-free survival with lower rates of pulmonary toxicity than in the ABVD arm, but other toxicities were high in the Stanford V arm.[7] This result was supported in the Eastern Cooperative Oncology Group (ECOG) phase 3 trial.[8] Finally, concerns over late toxicity mortality have led to the National Cancer Research Institute (NCRI) RAPID and RATHL trials, for which the BNLI has been the data center, and which use response adapted approaches for the treatment of patients with HL.

In this analysis of BNLI data, we assessed what this adds to the available UK cancer registry data. In the earlier time points, the registry data were incomplete.[9] In addition, although the registries can tell us about the improvement in overall survival, the BNLI database, which is much more extensive and had data that have been meticulously cleaned and validated, gives the opportunity to address not just the effect on survival of the more efficacious therapies but also the impact of reduced therapy-related deaths.

Patients and Methods

We looked at 6834 patients with a de novo diagnosis of HL who were registered onto studies with BNLI oversight from January 1, 1970, to December 31, 2009, with a date of final data collection of

Table 1 Trial and Study Participants Frequency Table

Trial Name (Disease Stage)	N (% Within Decade Group) for:				Total, N (% Within Cohort)
	1970s (N = 1701)	1980s (N = 2054)	1990s (N = 1690)	2000s (N = 1389)	N = 6834
MOPP vs. MOP (IV)	91 (5.3%)	0	0	0	91 (1.3%)
MOPP vs. B MOPP (IV)	139 (8.2%)	0	0	0	139 (2.0%)
LOPP vs. MOPP (III, IV)	50 (2.9%)	249 (12.1%)	0	0	299 (4.4%)
LOPP vs. LOPP/EVAP (III, IV)	0	594 (28.9%)	0	0	594 (8.7%)
LOPP/EVAP vs. LOPP/EVA (IB, IIB, III, IV)	0	0	169 (10.0%)	0	169 (2.5%)
PABIOE vs. CHLVPP/PABIOE (IB, IIB, III, IV)	0	0	638 (37.8%)	0	638 (9.3%)
Registration Pathology (I, II, III, IV)	1421 (83.6%)	1211 (59.0%)	659 (39.0%)	187 (13.5%)	3478 (50.9%)
HL in Young Adults 18-30 (I, II, III, IV)	0	0	0	21 (1.5%)	21 (0.3%)
LY07 (IA, IIA)	0	0	161 (9.5%)	64 (4.6%)	225 (3.3%)
PET/RAPID (IA, IIA)	0	0	0	541 (38.9%)	541 (7.9%)
RATHL (IB, IIB, III, IV + bulky IIA)	0	0	0	127 (9.1%)	127 (1.9%)
Stanford V (IB, IIB, III, IV + bulky IIA)	0	0	63 (3.7%)	449 (32.3%)	512 (7.5%)

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