Myocardial Infarction Mortality Risk After Treatment for Hodgkin Disease: A Collaborative British Cohort Study

Anthony J. Swerdlow, Craig D. Higgins, Paul Smith, David Cunningham, Barry W. Hancock, Alan Horwich, Peter J. Hoskin, Andrew Lister, John A. Radford, Ama Z. S. Rohatiner, David C. Linch

Background Myocardial infarction is a major cause of excess long-term mortality in survivors of Hodgkin disease, but limited information exists on the effects of specific chemotherapy regimens used to treat these patients on their risk of death from myocardial infarction.

Methods We followed a cohort of 7033 Hodgkin disease patients who were treated in Britain from November 1, 1967, through September 30, 2000, and compared their risk of myocardial infarction mortality with that in the general population of England and Wales. All statistical tests were two-sided.

Results A total of 166 deaths from myocardial infarction occurred in the cohort, statistically significantly more than expected (standardized mortality ratio [SMR] = 2.5, 95% confidence interval [CI] = 2.1 to 2.9), with an absolute excess risk of 125.8 per 100 000 person-years. Standardized mortality ratios decreased sharply with older age at first treatment, but absolute excess risks of death from myocardial infarction increased with older age up to age 65 years at first treatment. The statistically significantly increased risk of myocardial infarction mortality persisted through to 25 years after first treatment. Risks were increased statistically significantly and independently for patients who had been treated with supradiaphragmatic radiotherapy, anthracyclines, or vincristine. Risk was particularly high for patients treated with the doxorubicin, bleomycin, vinblastine, and dacarbazine regimen (SMR = 9.5, 95% CI = 3.5 to 20.6). Risk at 20 or more years after first treatment was particularly great for patients who had received supradiaphragmatic radiotherapy and vincristine without anthracylines (SMR = 14.8, 95% CI = 4.8 to 34.5).

Conclusions The risk of death from myocardial infarction after treatment for Hodgkin disease remains high for at least 25 years. The increased risks are related to supradiaphragmatic radiotherapy but may also be related to anthracycline and vincristine treatment.

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Cardiovascular disease is the most important cause of excess mortality, after second malignancy, in long-term survivors of Hodgkin disease (1–3). Myocardial infarction is the single most common cause of these cardiovascular disease deaths. Several cohort studies in North America and Europe have shown that patients who received mediastinal irradiation for Hodgkin disease had an increased risk of myocardial infarction mortality compared with the respective general populations, although the magnitude of this risk varied considerably (4). The relative risks of myocardial infarction mortality have generally been greater in men than in women and in patients treated when young than in patients treated at older ages. Although some studies (5–7) have analyzed risks of myocardial infarction mortality among Hodgkin disease patients in relation to chemotherapy overall, no study, to our knowledge, has examined these risks in association with specific regimens or drugs or for chemotherapy alone without mediastinal irradiation. Several of the drugs used to treat patients with Hodgkin disease are cardiotoxic; these include anthracyclines in particular, and also other drugs, including cyclophosphamide, etoposide, and vinca alkaloids (8).

Affiliations of authors: Sections of Epidemiology (AJS, CDH) and Radiotherapy (AH), Institute of Cancer Research, Sutton, UK; Gastrointestinal Unit, Royal Marsden Hospital, Sutton, UK (DC); Yorkshire Cancer Research Academic Unit of Clinical Oncology, Weston Park Hospital, Sheffield, UK (BWH); Cancer Centre, Mount Vernon Hospital, Middlesex, UK (PJH); Cancer Research UK Medical Oncology Unit, St Bartholomew's Hospital, London, UK (AL, ALSR); Cancer Research UK Department of Medical Oncology, Christie Hospital and The University of Manchester, Manchester, UK (JAR); Cancer Research UK and University College London Cancer Trials Centre (PS), and Department of Haematology (DCL), University College Hospital, London, UK.

Correspondence to: Anthony J. Swerdlow, DSc, Section of Epidemiology, Sir Richard Doll Building, Institute of Cancer Research, Sutton, Surrey SM2 5NG, UK (e-mail: anthony.swerdlow@icr.ac.uk).

See "Notes" following "References."

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To investigate risk factors associated with the risk of mortality from myocardial infarction, we conducted a cohort study of 7033 patients treated for Hodgkin disease.

Patients and Methods

Study Design and Data Collection

The study cohort comprised patients who were registered in the clinical databases of the British National Lymphoma Investigation (BNLI; a clinical trials collaboration among a large number of British hospitals), the Royal Marsden Hospital (London and Surrey, U.K.), St Bartholomew's Hospital (London, U.K.), and Christie Hospital (Manchester, U.K.). From each database, we extracted data on all British-resident patients who were recorded as having been treated for Hodgkin disease since the databases were established, with the following exceptions: patients entered into the Royal Marsden Hospital database before 1972 were excluded because we often lacked information on their cause of death and patients from the Christie Hospital database were limited to those who had participated in trials for which full data were available. Data on treatment, follow-up, and the cause of death extracted from the databases were completed and updated as necessary from case notes and by contact with the patient's general practitioner. The cohort members included from the BNLI were all participants in clinical trials who were diagnosed from March 1, 1970, through February 28, 1999, with follow-up to December 31, 1999. Cohort members from the Royal Marsden Hospital database were all patients diagnosed with Hodgkin disease from January 1, 1972, through March 31, 2000, with follow-up to March 31, 2000; cohort members from the St Bartholomew's Hospital database included all patients diagnosed with Hodgkin disease from November 1, 1967, through September 30, 2000, with follow-up to September 30, 2000; and cohort members from the Christie Hospital database were Hodgkin disease patients who participated in selected trials from October 1, 1974, through February 28, 1997, with follow-up to March 31, 2000. Cause of death was recorded in the databases, sometimes as a single underlying cause and sometimes as the sequence of causes recorded in the death certificate; in the latter case, we followed International Classification of Diseases (ICD) rules to determine the underlying cause of death. Deaths from myocardial infarction were defined as those with the code 410 in the ninth revision of ICD (ICD-9) (9) or its equivalent in other ICD revisions. This study was approved by the South East Multicentre Research Ethics Committee.

Statistical Analysis

For each patient within the cohort, we calculated the number of person-years at risk by sex, 5-year age-group, and calendar year, starting from the date of the first treatment and ending on the date of the end of follow-up, or on the date of the subject's 85th birthday, death, or other loss to follow-up, whichever occurred first. Follow-up was censored at age 85 years because beyond that age, certification of cause of death is likely to be inaccurate and national (i.e., expected) death rates by 5-year age-group are not available. For time-dependent variables (i.e., time since first treatment, attained age, and treatment modality), patients were allocated at each follow-up point in the analysis to the analytic category that applied to them at that time. Radiotherapy field was categorized as total nodal, subtotal nodal, mantle, other supradiaphragmatic, infradiaphragmatic, or unspecified. Chemotherapy was categorized according to the agent used. It was not practical to examine risks on a cohort basis in relation to dose or fractionation of treatments; those factors will be addressed elsewhere in a nested case–control study.

Expected numbers of deaths from myocardial infarction were calculated by multiplying the age-, sex-, and calendar-year–specific person-years at risk in the cohort by the corresponding mortality rates for the general population of England and Wales. We calculated standardized mortality ratios (SMRs) for myocardial infarction death as the ratio of the observed to the expected numbers of deaths; these ratios are sometimes referred to in the text as relative risks. Likelihood-based 95% confidence intervals (CIs) were calculated from Poisson models (10). All statistical tests were two-sided. Trend tests were performed as previously described (10). To calculate absolute excess risks, we subtracted the expected number of cases from the observed number of cases, divided the difference by the number of person-years at risk, and then multiplied by 100 000. We used the Kaplan–Meier method (11) to calculate cumulative (i.e., actuarial) risks. The analyses were conducted with the use of Stata statistical software (version 9.2; Stata Corporation, College Station, TX).

CONTEXT AND CAVEATS

Prior knowledge

Long-term survivors of Hodgkin disease have a higher risk of death from myocardial infarction than does the general population. However, the effects of specific chemotherapy regimens that are used to treat Hodgkin disease patients on their risk of death from myocardial infarction are unclear.

Study design

Collaborative British cohort study.

Contribution

The risk of death from myocardial infarction among Hodgkin disease patients was two and a half times that in the general population. Increased risks persisted for at least 25 years after treatment. The risk of myocardial infarction mortality was increased for Hodgkin disease patients who had been treated with supradiaphragmatic radiotherapy, anthracyclines, or vincristine.

Limitations

The analyses did not take into account potential differences in nontherapeutic risk factors for myocardial infarction between the cohort or specific treatment groups and the general population. The risks associated with specific chemotherapy agents could not be estimated with certainty because different agents are frequently used in combination.

Implications

Additional studies in other cohorts and/or case–control studies are needed to clarify the association between specific chemotherapeutic agents and regimens and myocardial infarction mortality.

Results

Of the 7033 patients included in the study cohort, 62% were male and 35% were first treated before 1980 (Table 1); 31% were

Table 1. Descriptive characteristics of cohort*

Characteristic	No. of subjects	Person-years†
Sex		
Male	4353	48136
Female	2680	30246
Year of first treatment		
Before 1975	1000	16358
1975–1979	1434	21791
1980–1984	1190	15210
1985–1989	1456	14493
1990 or later	1953	10529
Age at first treatment, y		
<25	2158	28500
25–34	2014	23843
35–44	1140	12525
45–54	766	7355
55–64	630	4652
≥65	325	1507
Treatment center or collaborative group		
British National Lymphoma Investigation	4477	48837
Royal Marsden Hospital	962	11423
St Bartholomew's Hospital	828	10702
Christie Hospital	766	7421
Type of treatment‡		
Total nodal irradiation§	290	4136
Subtotal nodal irradiation, but not total nodal irradiation	134	1987
Mantle radiotherapy, but not total or subtotal nodal irradiation	1969	24273
Other supradiaphragmatic radiotherapy, but not total or subtotal nodal or mantle radiotherapy	1069	10429
Unknown-field radiotherapy, but none known to be supradiaphragmatic	1325	12542
Infradiaphragmatic radiotherapy, but none supradiaphragmatic or of unknown field	249	2254
LOPP	2160	18009
MOPP	1151	13346
ChlVPP	987	9271
MVPP	829	10289
EVAP	862	6863
PABLOE	627	2732
ABVD	385	1760
Total	7033	78382

* LOPP = chlorambucil, vincristine, procarbazine, prednisone; MOPP = mechlorethamine, vincristine, procarbazine, prednisone; ChlVPP = chlorambucil, vinblastine, procarbazine, prednisolone; MVPP = mechlorethamine, vinblastine, procarbazine, prednisone; EVAP = etoposide, vinblastine, Adriamycin (doxorubicin), prednisone; PABLOE = prednisone, Adriamycin (doxorubicin), bleomycin, vincristine, etoposide; ABVD = Adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine.

† Number of person-years for some categories do not exactly total 78382 because of rounding.

‡ Person-years were calculated as a time-dependent variable (see "Patients and Methods"). The chemotherapy regimens displayed are the most common ones, and the numbers of subjects are not mutually exclusive—individuals may be included in more than one chemotherapy category.

§ Includes five patients treated with total-body irradiation.

Table 2. Risk of death from myocardial infarction by sex, age at first treatment, time since first treatment, year of treatment, and attained age*

Risk factor	No. of deaths	SMR (95% CI)	*P*†	AER
Sex				
Male	138	2.5 (2.1 to 3.0)	<.001	173.6
Female	28	2.2 (1.4 to 3.1)	<.001	49.7
Age at first treatment, y				
<25	17	18.7 (10.9 to 29.9)	<.001	56.5
25–34	22	5.9 (3.7 to 9.0)	<.001	76.7
35–44	21	2.6 (1.6 to 4.0)	<.001	103.5
45–54	44	2.6 (1.9 to 3.5)	<.001	365.7
55–64	43	1.8 (1.3 to 2.4)	<.001	411.5
≥65	19	1.4 (0.8 to 2.2)	.21	346.9
Time since first treatment, y				
<1	23	4.2 (2.7 to 6.3)	<.001	257.1
1–4	30	1.7 (1.1 to 2.4)	.01	46.3
5–9	41	2.3 (1.6 to 3.1)	<.001	109.1
10–14	25	1.9 (1.2 to 2.8)	.004	85.3
15–19	32	4.1 (2.8 to 5.8)	<.001	288.8
20–24	12	3.1 (1.6 to 5.4)	.002	196.8
≥25	3	2.8 (0.6 to 8.3)	.18	221.5
Calendar year of first treatment				
Before 1975	49	2.6 (1.9 to 3.4)	<.001	182.3
1975–1979	64	3.2 (2.4 to 4.0)	<.001	201.0
1980–1984	24	1.8 (1.1 to 2.6)	.01	68.2
1985 or later	29	2.0 (1.4 to 2.9)	<.001	58.4
Attained age, y				
<45	30	8.5 (5.7 to 12.1)	<.001	50.5
45–54	36	3.8 (2.7 to 5.2)	<.001	196.8
55–64	50	2.6 (1.9 to 3.4)	<.001	404.8
65–74	36	1.5 (1.1 to 2.1)	.02	312.5
75–84	14	1.2 (0.7 to 2.1)	.52	256.4
Total cohort	166	2.5 (2.1 to 2.9)	<.001	125.8

* SMR = standardized mortality ratio; CI = confidence interval; AER = absolute excess risk per 100000 person-years.

† Two-sided, based on Poisson distribution.

younger than 25 years when first treated, 45% were 25–44 years old, and 24% were 45 years or older. A total of 64% of the cohort members were registered in the BNLI database, and 11%–14% were registered in the databases of each of the Royal Marsden, St Bartholomew's, and Christie hospitals. During follow-up, 2441 cohort members died, 27 were censored when they reached the age of 85 years, 66 emigrated, and 255 (3.6%) were otherwise lost to follow-up, leaving 4244 cohort members who were alive at the end of follow-up for their subcohort (see "Patients and Methods"). Follow-up was for a total of 78 382 person-years, or an average of 11.1 years per study subject. The cause of death was ascertained for 2424 (99.3%) of the subjects who died; 166 of these deaths were due to myocardial infarction.

The relative risk of death from myocardial infarction in this cohort was statistically significantly increased more than twofold compared with the general population (SMR = 2.5, 95% CI = 2.1 to 2.9) and was slightly higher in males than in females (Table 2). By contrast, the absolute excess risk of death from myocardial infarction, which was 125.8 per 100000 person-years for the

Table 3. Risk of death from myocardial infarction by age at first treatment and attained age*

	Attained age (y)											
	45–54				55–64				65–74			
Age at first treatment (y)	No. of deaths	SMR (95% CI)	P†	AER	No. of deaths	SMR (95% CI)	P†	AER	No. of deaths	SMR (95% CI)	P†	AER
<35	13	6.7 (3.6 to 11.5)	<.001	236	0	0 (0 to 11.8)	1.00	–	–	–	–	–
35–44	8	2.1 (0.9 to 4.2)	.08	74	8	3.1 (1.3 to 6.1)	.01	324	1	2.1 (0.05 to 11.8)	.75	340
45–54	15	4.0 (2.2 to 6.6)	<.001	362	21	2.5 (1.5 to 3.8)	<.001	378	8	1.9 (0.8 to 3.7)	.13	428
55–64	–	–	–	–	21	2.7 (1.7 to 4.1)	<.001	571	17	1.4 (0.8 to 2.2)	.24	233
≥65	–	–	–	–	–	–	–	–	10	1.2 (0.5 to 2.4)	.27	371

* SMR = standardized mortality ratio; CI = confidence interval; AER = absolute excess risk per 100 000 person-years; – = not applicable.

† Two-sided test based on Poisson distribution.

cohort overall, was more than three times higher in males than in females. The relative risk of death from myocardial infarction for the entire cohort was unaltered when we censored follow-up at the occurrence of a second malignancy (SMR = 2.5, 95% CI = 2.1 to 2.9; data not shown). The relative risk of death from myocardial infarction decreased sharply with older age at first treatment and was only slightly and non–statistically significantly increased in the oldest age-at-first-treatment group (i.e., cohort members who were 65 years or older) compared with the general population (Table 2). However, the absolute excess risks of death from myocardial infarction increased steadily with older age at first treatment except beyond age 65 years at first treatment. The relative risk of death from myocardial infarction decreased with attained age, but the absolute excess risks did not change in a consistent way.

We also examined the association between attained age and the relative risk of death from myocardial infarction separately for males and females to see if there was any evidence for an effect of menopause on risk. We did not have data on the menopausal status of the female members of the cohort; instead, we used an attained-age cut point of 50 years as a proxy for menopause (12). In females, the standardized mortality ratio at attained ages younger than 50 years was 9.6 (95% CI = 3.5 to 20.8) and that at older attained ages was 1.8 (95% CI = 1.1 to 2.7); in males, the corresponding standardized mortality ratios were 6.0 (95% CI = 4.3 to 8.1) and 2.1 (95% CI = 1.7 to 2.5), respectively (data not shown). Thus, standardized mortality ratios were reduced with older age to a greater extent in women than in men when a cut point at the approximate age of menopause was used, although the difference in reduction was not statistically significant ($P = .22$).

During the first year after the start of treatment, the relative risk of death from myocardial infarction for this cohort was statistically significantly increased by approximately fourfold compared with the general population; the risk was approximately twofold higher during years 1 through 14 after the start of treatment, peaked again at approximately fourfold higher during years 15 through 19 after treatment, and remained statistically significantly threefold higher during years 20 through 24 after the start of treatment. Risk of death from myocardial infarction was greatest for patients who were first treated for Hodgkin disease before 1980; however, the risks were also statistically significantly increased for those who were first treated more recently (Table 2). The 20-year cumulative risks of myocardial infarction mortality were 1.8% (95% CI = 1.2% to 2.6%) for patients who were younger than 35 years at first treatment for Hodgkin disease, 7.4% (95% CI = 5.6% to 9.9%) for patients who were 35–54 years old at first treatment, and 23.6% (95% CI = 16.2% to 33.5%) for patients who were 55 years or older at first treatment.

We examined risk with respect to both age at first treatment and attained age (Table 3) and found that there was inconsistent evidence for a decrease in relative risk with older attained age within age-at-first-treatment strata and only slight evidence for a decrease in relative risk with older age at first treatment within strata of attained age. Absolute excess risks showed no consistent pattern with either age parameter (Table 3).

We next examined the risk of mortality from myocardial infarction by treatment. The risk of death from myocardial infarction was increased statistically significantly in patients who had received total nodal irradiation (SMR = 8.9, 95% CI = 5.4 to 13.8), mantle radiotherapy (SMR = 3.2, 95% CI = 2.3 to 4.2), other supradiaphragmatic radiotherapy (SMR = 1.9, 95% CI = 1.2 to 2.9), or radiotherapy to unknown fields (SMR = 2.3, 95% CI = 1.4 to 3.6) but not for patients who had received infradiaphragmatic radiotherapy alone (SMR = 1.2, 95% CI = 0.4 to 2.8) (Table 4). Patients who had received subtotal nodal radiotherapy had a non–statistically significantly increased risk of death from myocardial infarction (SMR = 2.6, 95% CI = 0.8 to 6.0) that was based on small numbers (Table 4). The risk of death from myocardial infarction was statistically significantly increased for patients who had received anthracyclines (SMR =2.9, 95% CI = 1.9 to 4.3), especially those who were treated with the doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) regimen (SMR = 9.5, 95% CI = 3.5 to 20.6). In addition, many other regimens and individual chemotherapeutic agents were associated with statistically significantly increased risks of death from myocardial infarction. When the analyses were confined to patients who had not received supradiaphragmatic radiotherapy (Table 4), there remained statistically significantly increased risks associated with all the chemotherapeutic regimens and agents that were statistically significantly increased in the overall analyses.

We next analyzed the risk of death from myocardial infarction among individuals who had received chemotherapy without supradiaphragmatic radiotherapy or anthracyclines (Table 4). Both the numbers of subjects under analysis and the standardized mortality ratios were reduced: the only statistically significant relative risks were for patients who had received vincristine (SMR = 2.0, 95%

Table 4. Risk of death from myocardial infarction by treatment modality*

Treatment modality	Chemotherapy with supradiaphragmatic radiotherapy† (n = 3052; median follow-up = 7.9 y)			Chemotherapy without supradiaphragmatic radiotherapy† (n = 3933; median follow-up = 2.7 y)			Chemotherapy without supradiaphragmatic radiotherapy or anthracyclines† (n = 2189; median follow-up = 2.2 y)			Radiotherapy without anthracyclines (n = 3590; median follow-up = 12.3 y)			Total, all patients (n = 7033; median follow-up = 9.9 y)		
	No. of deaths	SMR (95% CI)	P‡	No. of deaths	SMR (95% CI)	P‡	No. of deaths	SMR (95% CI)	P‡	No. of deaths	SMR (95% CI)	P‡	No. of deaths	SMR (95% CI)	P‡
Radiotherapy															
Total nodal (n = 290)	–	–	–	–	–	–	–	–	–	19	9.0 (5.4 to 14.1)	<.001	20	8.9 (5.4 to 13.8)	<.001
Subtotal nodal, no total nodal (n = 134)	–	–	–	–	–	–	–	–	–	5	2.6 (0.9 to 6.2)	.09	5	2.6 (0.8 to 6.0)	.10
Mantle, no total or subtotal nodal (n = 1969)	–	–	–	–	–	–	–	–	–	45	3.2 (2.3 to 4.3)	<.001	47	3.2 (2.3 to 4.2)	<.001
Other supradiaphragmatic, no mantle or total or subtotal nodal (n = 1069)	–	–	–	–	–	–	–	–	–	19	1.9 (1.2 to 3.0)	.01	21	1.9 (1.2 to 2.9)	.01
Unknown field, no known supradiaphragmatic (n = 1325)	–	–	–	–	–	–	–	–	–	18	2.3 (1.4 to 3.7)	.002	20	2.3 (1.4 to 3.6)	.001
Infradiaphragmatic only (n = 249)	–	–	–	–	–	–	–	–	–	2	0.5 (0.1 to 1.9)	.56	5	1.2 (0.4 to 2.8)	.80
Chemotherapy regimens															
LOPP (n = 2160)	14	2.8 (1.5 to 4.6)	.002	16	2.4 (1.3 to 3.8)	.004	8	2.6 (1.1 to 5.1)	.03	–	–	–	30	2.5 (1.7 to 3.6)	<.001
MOPP (n = 1151)	25	5.4 (3.5 to 7.9)	<.001	17	1.8 (1.0 to 2.9)	.03	16	1.7 (1.0 to 2.8)	.05	–	–	–	42	3.0 (2.1 to 4.0)	<.001
ChlVPP (n = 987)	5	1.9 (0.6 to 4.5)	.24	5	1.3 (0.4 to 3.1)	.67	2	0.7 (0.1 to 2.5)	.89	–	–	–	10	1.6 (0.8 to 2.9)	.23
MVPP (n = 829)	9	2.9 (1.3 to 5.5)	.01	11	12.1 (1.1 to 3.8)	.03	6	1.2 (0.5 to 2.7)	.71	–	–	–	20	2.4 (1.5 to 3.7)	<.001
EVAP (n = 862)	3	2.4 (0.5 to 7.0)	.27	5	1.9 (0.6 to 4.5)	.25	–	–	–	–	–	–	8	2.1 (0.9 to 4.1)	.09
PABLOE (n = 627)	0	0 (0 to 18.5)	1.00	1	1.4 (0.04 to 8.1)	1.0	–	–	–	–	–	–	1	1.1 (0.03 to 6.3)	1.0
ABVD (n = 385)	3	12.1 (2.5 to 35.3)	.004	3	7.8 (1.6 to 22.7)	.01	–	–	–	–	–	–	6	9.5 (3.5 to 20.6)	<.001
Chemotherapy agents															
Vincristine (n = 4048)	39	3.7 (2.6 to 5.1)	<.001	39	2.2 (1.6 to 3.0)	<.001	25	2.0 (1.3 to 2.9)	.003	–	–	–	78	2.8 (2.2 to 3.5)	<.001
Vinblastine (n = 3512)	19	2.6 (1.5 to 4.0)	<.001	24	1.8 (1.2 to 2.8)	.008	9	1.1 (0.5 to 2.0)	.92	–	–	–	43	2.1 (1.5 to 2.8)	<.001
All vinca alkaloids (n = 5451)	48	3.1 (2.3 to 4.1)	<.001	50	2.0 (1.5 to 2.6)	<.001	33	1.6 (1.1 to 2.3)	.01	–	–	–	98	2.4 (1.9 to 2.9)	<.001
Mustine (n = 2005)	33	4.2 (2.9 to 5.9)	<.001	28	1.9 (1.2 to 2.7)	.003	22	1.5 (1.0 to 2.3)	.07	–	–	–	61	2.7 (2.1 to 3.5)	<.001
Procarbazine (n = 4769)	48	3.2 (2.4 to 4.3)	<.001	48	1.9 (1.4 to 2.6)	<.001	32	1.6 (1.1 to 2.3)	.02	–	–	–	96	2.4 (2.0 to 3.0)	<.001
Prednisone (n = 5236)	48	3.1 (2.3 to 4.2)	<.001	49	2.0 (1.5 to 2.6)	<.001	32	1.6 (1.1 to 2.3)	.01	–	–	–	97	2.4 (2.0 to 3.0)	<.001
Chlorambucil (n = 3126)	20	2.5 (1.6 to 3.9)	<.001	22	2.1 (1.3 to 3.1)	.003	10	1.6 (0.8 to 2.9)	.21	–	–	–	42	2.3 (1.6 to 3.1)	<.001
Etoposide (n = 2601)	6	2.1 (0.8 to 4.5)	.15	15	2.9 (1.6 to 4.8)	<.001	1	3.8 (0.1 to 21.1)	.46	–	–	–	21	2.6 (1.6 to 4.0)	<.001
Adriamycin (doxorubicin) (n = 2654)	7	2.4 (1.0 to 5.0)	.05	16	3.2 (1.8 to 5.1)	<.001	–	–	–	–	–	–	23	2.9 (1.8 to 4.3)	<.001
Epirubicin (n = 226)	0	0 (0 to 20.6)	1.00	1	3.8 (0.1 to 21.2)	.46	–	–	–	–	–	–	1	2.3 (0.1 to 12.6)	.71
All anthracyclines (n = 2826)	7	2.3 (0.9 to 4.8)	.07	17	3.2 (1.9 to 5.2)	<.001	–	–	–	–	–	–	24	2.9 (1.9 to 4.3)	<.001
Bleomycin (n = 1522)	4	3.1 (0.8 to 7.8)	.09	7	3.4 (1.4 to 7.0)	.01	0	0 (0 to 8.9)	1.00	–	–	–	11	3.3 (1.6 to 5.9)	.001
Cyclophosphamide (n = 377)	1	2.0 (0.1 to 11.2)	.78	1	2.2 (0.1 to 12.3)	.73	0	0 (0 to 23.6)	1.00	–	–	–	2	2.1 (0.3 to 7.6)	.49

* SMR = standardized mortality ratio; CI = confidence interval; – = not applicable; LOPP = chlorambucil, vincristine, procarbazine, prednisone; MOPP = mechlorethamine, vincristine, procarbazine, prednisone; ChlVPP = chlorambucil, vinblastine, procarbazine, prednisolone; MVPP = mechlorethamine, vinblastine, procarbazine, prednisone; EVAP = etoposide, vinblastine, Adriamycin (doxorubicin), prednisone; PABLOE = prednisone, Adriamycin (doxorubicin), bleomycin, vincristine, etoposide; ABVD = Adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine; n = number of subjects who contributed any person-years in that category; median follow-up = median follow-up time spent in that category.

† Supradiaphragmatic radiotherapy category includes total nodal, subtotal nodal, mantle, other supradiaphragmatic, and unknown-field radiotherapy.

‡ Two-sided, based on Poisson distribution.

CI = 1.3 to 2.9), procarbazine (SMR = 1.6, 95% CI = 1.1 to 2.3), prednisone (SMR = 1.6, 95% CI = 1.1 to 2.3), or the combination of chlorambucil, vincristine, procarbarzine, and prednisone (LOPP; SMR = 2.6, 95% CI = 1.1 to 5.1). We observed borderline statistically significant relative risks for patients who had received mechlorethamine, vincristine, procarbazine, and prednisone (MOPP; SMR = 1.7, 95% CI = 1.0 to 2.8) or mustine (SMR = 1.5, 95% CI = 1.0 to 2.3). The standardized mortality ratio for patients treated with vinblastine was not increased (1.1, 95% CI = 0.5 to 2.0). The relative risks for patients who had received procarbazine or prednisone but not vincristine, anthracyclines, or supradiaphragmatic radiotherapy were not increased (SMR = 1.0 [95% CI = 0.4 to 2.0] and 1.0 [95% CI = 0.4 to 2.0], respectively) (data not shown). It was not possible to analyze the risk of death from myocardial infarction for patients who received vincristine but not procarbazine or prednisone because very few subjects had received that treatment.

We next examined the relative risk of death from myocardial infarction according to the length of time since the first treatment with selected treatment modalities. The increased risk for patients treated with anthracyclines overall was largely during the year after first treatment, with non–statistically significantly increased risks and few person-years (data not shown) in subsequent years (Table 5). Patients who were treated with vincristine overall had statistically significantly increased risks of death from myocardial infarction throughout follow-up; those risks were highest during the first year after the start of treatment and at 20 years or longer after treatment. The risk of death from myocardial infarction among patients who received radiotherapy increased steadily throughout follow-up. The risks among patients who had received both supradiaphragmatic radiotherapy and vincristine without anthracyclines increased sharply after the first year of follow-up, reaching an SMR of 14.8 (95% CI = 4.8 to 34.5) at 20 years or longer after treatment.

Finally, we examined the risk of death from myocardial infarction according to the patient's age at first treatment with the selected treatment modalities. For almost all treatment modalities listed in Table 6, the relative risk decreased with increasing age at first treatment; the highest risk was for patients who were younger than 35 years at first treatment with anthracyclines, but the risks were also high for those treated with vincristine or supradiaphragmatic radiotherapy before age 35 years. When we subdivided the cohort further by age at first treatment, the standardized mortality ratios for patients who were younger than 25 years at first treatment with any supradiaphragmatic radiotherapy, anthracyclines, or vincristine were 22.6 (95% CI = 12.6 to 37.2), 55.7 (95% CI = 6.7 to 201.1), and 27.6 (95% CI = 11.9 to 54.3), respectively, whereas for patients who were 65 years or older at first treatment, they were 1.4 (95% CI = 0.7 to 2.5), 1.0 (95% CI = 0.1 to 3.5), and 1.4 (95% CI = 0.6 to 2.6), respectively (data not shown). The vincristine-related increased myocardial infarction mortality risk at ages under 35 years, unlike that with anthracyclines, was restricted to patients who had also received supradiaphragmatic radiotherapy.

Discussion

As has been reported in other large cohort studies of Hodgkin disease patients (1,5), we also found that the risk of myocardial infarction mortality was statistically significantly increased in our study cohort compared with the general population. The overall relative risk of death from myocardial infarction was at the lower end of the range of risks that have been reported in the literature (4); however, because risks vary greatly by age, type of treatment, and length of follow-up, comparisons of risks between studies are informative only if these variables are taken into account. We found that the relative risk of death from myocardial infarction was slightly greater in men than in women; a similar finding was reported in one previous study (6) but not in another study (1). We found that the risk of death from myocardial infarction was high in the year after first treatment, peaked 15–19 years after treatment was first received and remained statistically significantly increased 20–24 years after treatment, with some evidence suggesting that the increased risk may persist for even 25 years or longer after treatment. Hancock et al. (5) found statistically significantly increased relative risks in the first 5 years after initial treatment, and those risks increased further with longer follow-up to a maximum risk at 20 years or more of follow-up. Aleman et al. (1) found increased risks in the first 5 years (but based on only two deaths) and the risk peaked at 21–25 years with a decline thereafter, also based on small numbers.

Most (4), but not all (1,7), of the previous literature on myocardial infarction mortality in patients treated for Hodgkin disease have reported that the relative risk of myocardial infarction mortality decreases with increasing age at first treatment. We found a similar association in our comparatively larger cohort. However, we also found that absolute excess risks of death from myocardial infarction increased with increasing age at first treatment, up to age 65 years at first treatment. Previous smaller cohort studies (1, 6) also found greater absolute excess risks with older age at first treatment but did not provide absolute excess risk data for patients who were older than 65 years at first treatment.

We also found, as reported in previous studies (4), that the relative risk of death from myocardial infarction decreased with older attained age, a finding that reflects the much lower background risks of death from myocardial infarction at younger versus older ages in the general population (i.e., comparison group). However, the absolute excess risk, which might be of greater relevance to individual patients, peaked for patients aged 55–64 years and was lower for older patients. One previous study (6) found no such peak in patients younger than 70 years, whereas another study (1) found that the absolute excess risk peaked at ages 36–45 years (1), although the latter finding was based on small numbers.

We found that the patients in our study cohort who had received total nodal irradiation or mantle radiotherapy had statistically significantly several-fold increased risks of death from myocardial infarction compared with the general population. A large literature has documented the widespread cardiovascular complications of high-dose mediastinal radiotherapy (2,4–6,13,14). The greater relative risks that we observed among patients who received total nodal irradiation than among patients who received mantle radiotherapy may reflect the fact that the former treatment includes a greater volume of the heart within the radiation field as well as overlapping radiation fields across the heart. In addition, total nodal irradiation virtually ceased to be used as a treatment in this

Table 5. Risk of death from myocardial infarction by selected treatment modality and time since first treatment*

Time since start of first treatment (y)	Treatment modality: With supradiaphragmatic radiotherapy — Anthracyclines: No. of deaths	SMR (95% CI)	P†	Vincristine, no anthracyclines: No. of deaths	SMR (95% CI)	P†	No chemotherapy: No. of deaths	SMR (95% CI)	P†	Without supradiaphragmatic radiotherapy — Anthracyclines: No. of deaths	SMR (95% CI)	P†
<1	1	2.3 (0.1 to 12.7)	.71	6	7.6 (2.8 to 16.4)	<.001	5	2.8 (0.9 to 6.4)	.07	10	10.8 (5.2 to 19.8)	<.001
1–9	4	1.8 (0.5 to 4.5)	.39	11	2.5 (1.2 to 4.5)	.01	25	2.1 (1.4 to 3.1)	<.001	6	1.7 (0.6 to 3.6)	.32
10–19	2	7.2 (0.9 to 26.2)	.06	12	4.9 (2.5 to 8.6)	<.001	26	3.4 (2.2 to 5.0)	<.001	1	1.4 (0.04 to 8.0)	1.00
≥20	0	0 (0 to 694)	1.00	5	14.8 (4.8 to 34.5)	<.001	6	2.7 (1.0 to 6.0)	.05	0	0 (0 to 170.5)	1.00
Total	7	2.3 (0.9 to 4.8)	.07	34	4.3 (3.0 to 6.0)	<.001	62	2.7 (2.0 to 3.4)	<.001	17	3.2 (1.9 to 5.2)	<.001
		P_{trend} = .30			P_{trend} = .13			P_{trend} = .32			P_{trend}<.001	

* Supradiaphragmatic radiotherapy category includes total nodal, subtotal nodal, mantle, other supradiaphragmatic, and unknown-field radiotherapy. SMR = standardized mortality ratio; CI = confidence interval.

† Two-sided test based on Poisson distribution.

cohort 20 years ago, whereas mantle treatment continued throughout the study period: the longer average follow-up of patients who received total nodal irradiation would tend to yield greater standardized mortality ratios because radiotherapy-related standardized mortality ratios increase with the length of follow-up.

Patients who had received other supradiaphragmatic radiotherapy also had an increased risk of death from myocardial infarction, but the magnitude of their increased risk was lower than that for patients who received total nodal irradiation or mantle radiotherapy, likely reflecting the mixed nature of the exposures from these treatments, some of which involved the mediastinum but many of which did not. Similarly, the modestly increased risk we observed for patients who received radiotherapy to an unknown field likely reflects the fact that the majority of radiotherapy for Hodgkin disease is supradiaphragmatic. Relatively few of the patients in our study cohort had been treated with subtotal nodal irradiation, and the non–statistically significantly increased risk for this treatment had a wide confidence interval. Our data on mortality by duration since treatment indicate that the increased risks of death from myocardial infarction related to radiotherapy persist for at least 20–24 years after treatment.

Our study has several limitations. Some of the results are based on small numbers. Also, major risk factors for myocardial infarction, such as smoking history, blood pressure, and serum lipid levels, are potential confounders for our results if these variables differed between the cohort or specific treatment groups and the general population. We were not able to adjust the standardized mortality ratios for other risk factors associated with myocardial infarction (nor were authors of other large cohort studies of Hodgkin disease patients), but we believe that there is no obvious reason why these factors should vary substantially between Hodgkin disease patients and the general population. Some issues preclude a definitive interpretation of our results that suggest that certain chemotherapeutic agents may cause death from myocardial infarction. First, our analyses of specific agents are potentially subject to a high degree of confounding because the use of different agents is often highly correlated; therefore, statistical adjustment cannot be used to discriminate between agents because of colinearity. Second, there are no similar published long-term data for Hodgkin disease patients on myocardial infarction mortality by chemotherapeutic agent and regimen with which to inform interpretation. Previous large cohort studies of Hodgkin disease patients have analyzed the risk of death from myocardial infarction only in relation to chemotherapy overall and not to specific agents; one study (7) found a lower risk of myocardial infarction mortality after chemotherapy than after mediastinal irradiation, whereas another

Table 6. Risk of death from myocardial infarction by selected treatment modality and age at first treatment*

Age at first treatment (y)	Treatment modality: With supradiaphragmatic radiotherapy — Anthracyclines: No. of deaths	SMR (95% CI)	P†	Vincristine, no anthracyclines: No. of deaths	SMR (95% CI)	P†	No chemotherapy: No. of deaths	SMR (95% CI)	P†	Without supradiaphragmatic radiotherapy — Anthracyclines: No. of deaths	SMR (95% CI)	P†
<35	4	23.7 (6.5 to 60.7)	<.001	12	16.7 (8.7 to 29.2)	<.001	15	8.5 (4.7 to 14.0)	<.001	3	19.7 (4.1 to 57.6)	.001
35–54	2	1.8 (0.2 to 6.6)	.60	15	4.8 (2.7 to 8.0)	<.001	19	2.4 (1.4 to 3.7)	.001	7	5.0 (2.0 to 10.2)	.001
≥55	1	0.6 (0.01 to 3.2)	.97	7	1.7 (0.7 to 3.5)	.25	28	2.1 (1.4 to 3.0)	<.001	7	1.9 (0.8 to 3.9)	.17
Total	7	2.3 (0.9 to 4.8)	.07	34	4.3 (3.0 to 6.0)	<.001	62	2.7 (2.0 to 3.4)	<.001	17	3.2 (1.9 to 5.2)	<.001
		P_{trend}<.001			P_{trend}<.001			P_{trend}<.001			P_{trend}<.001	

* Supradiaphragmatic radiotherapy includes total nodal, subtotal nodal, mantle, other supradiaphragmatic, and unknown-field radiotherapy. SMR = standardized mortality ratio; CI = confidence interval.

† Two-sided test based on Poisson distribution.

Vincristine, no anthracyclines			Anthracyclines			Total Vincristine			Supradiaphragmatic radiotherapy		
No. of deaths	SMR (95% CI)	P†	No. of deaths	SMR (95% CI)	P†	No. of deaths	SMR (95% CI)	P†	No. of deaths	SMR (95% CI)	P†
7	5.0 (2.0 to 10.2)	.001	11	8.8 (4.4 to 15.8)	<.001	20	6.9 (4.2 to 10.7)	<.001	5	1.8 (0.6 to 4.2)	.31
12	1.8 (0.9 to 3.1)	.08	10	1.7 (0.8 to 3.1)	.16	31	1.9 (1.3 to 2.7)	.002	49	2.4 (1.8 to 3.2)	<.001
4	1.0 (0.3 to 2.7)	1.00	3	2.9 (0.6 to 8.5)	.17	20	2.7 (1.6 to 4.1)	<.001	46	3.6 (2.7 to 4.9)	<.001
2	2.2 (0.3 to 7.9)	.46	0	0 (0 to 135.7)	1.00	7	5.3 (2.1 to 11.0)	<.001	13	4.3 (2.3 to 7.4)	<.001
25	2.0 (1.3 to 2.9)	.003	24	2.9 (1.9 to 4.3)	<.001	78	2.8 (2.2 to 3.5)	<.001	113	2.9 (2.4 to 3.5)	<.001
	P_{trend} = .06			P_{trend} = .004			P_{trend} = .33			P_{trend} = .01	

study (6) found somewhat lower risks after chemotherapy plus mediastinal radiation than after mediastinal radiation alone, probably due to lower dose and smaller radiation field size in the combined modality setting (6).

We found that the statistically significantly increased myocardial infarction mortality risks associated with several chemotherapeutic treatment regimens and agents persisted even when we excluded the one well-established therapeutic cause of myocardial infarction mortality in Hodgkin disease patients, supradiaphragmatic radiotherapy, from the analysis. On the basis of the previous literature (4) and the magnitudes of risks observed in our cohort, we conclude that the most likely chemotherapeutic cause of increased risk of death from myocardial infarction is treatment with anthracyclines.

A considerable body of work has shown that anthracyclines can lead to acute toxic cardiomyopathy (4,8). Various chronic cardiac complications have been described in children who have been treated with anthracyclines (4). In addition, some cases of late cardiac death after apparent recovery from anthracycline-induced heart failure have been noted in adults (15), and very high standardized mortality ratios for "clinical cardiac events" after treatment with anthracyclines, especially mitoxantrone and doxorubicin, were reported in a cohort of 476 adult patients in Mexico (16). However, to our knowledge, there has not been an analysis of the long-term risks of myocardial infarction mortality or incidence after anthracycline treatment for Hodgkin disease. Moser et al. (17) reported that in patients with non-Hodgkin lymphoma who were treated with doxorubicin-based chemotherapy, the long-term risk of myocardial infarction incidence was not increased for follow-up overall but was, on the basis of much smaller numbers than our study, statistically significantly increased beyond 5 years after treatment. However, the non-Hodgkin lymphoma patients in that study were, in general, considerably older than the patients in our study cohort, and our data showed that anthracycline-related relative risks were much higher for patients who were treated at younger versus older ages. In addition, our data were for myocardial infarction mortality, not incidence, and thus, our results would be affected by any adverse effect of chemotherapeutic agents on survival after myocardial infarction as well as by effects on myocardial infarction occurrence. The particularly high risks of death from myocardial infarction in our study cohort after treatment with the ABVD regimen might reflect effects on myocardial infarction mortality of right heart strain resulting from the pulmonary effects of bleomycin, as well as the cardiac effects of doxorubicin. The reason why myocardial infarction mortality risk was greater after ABVD than after PABLOE (prednisone,

Vincristine, no anthracyclines			Anthracyclines			Total Vincristine			Supradiaphragmatic radiotherapy		
No. of deaths	SMR (95% CI)	P†	No. of deaths	SMR (95% CI)	P†	No. of deaths	SMR (95% CI)	P†	No. of deaths	SMR (95% CI)	P†
1	1.7 (0.04 to 9.6)	0.88	7	20.9 (8.4 to 43.1)	<.001	18	10.9 (6.5 to 17.2)	<.001	34	10.1 (7.0 to 14.1)	<.001
5	1.0 (0.3 to 2.3)	1.00	9	3.5 (1.6 to 6.6)	.003	28	2.6 (1.8 to 3.8)	<.001	43	2.9 (2.1 to 3.9)	<.001
19	2.7 (1.6 to 4.2)	<.001	8	1.5 (0.6 to 2.9)	.35	32	2.0 (1.4 to 2.8)	<.001	36	1.8 (1.2 to 2.4)	.003
25	2.0 (1.3 to 2.9)	.003	24	2.9 (1.9 to 4.3)	<.001	78	2.8 (2.2 to 3.5)	<.001	113	2.9 (2.4 to 3.5)	<.001
	P_{trend} = .07			P_{trend}<.001			P_{trend}<.001			P_{trend}<.001	

doxorubicin, bleomycin, vincristine, etoposide), the other main regimen containing bleomycin and doxorubicin in our cohort, may be that ABVD was virtually always given alone (i.e., as six cycles), whereas PABLOE was generally part of an alternating regimen, so that only three cycles were usually given.

Our analysis of other chemotherapies in patients who had not received supradiaphragmatic radiotherapy or anthracyclines revealed that vincristine, procarbazine, prednisone, and regimens that contain all these agents (i.e., LOPP and MOPP) were associated with statistically significantly or borderline statistically significantly increased risks of death from myocardial infarction; the risks were especially increased for vincristine and LOPP. There is published evidence for the cardiotoxicity of vincristine but not of procarbazine or prednisone (8). Further evidence from our study suggesting that vincristine rather than procarbazine or prednisone was responsible for the increased risk is that myocardial infarction mortality risks associated with procarbazine and prednisone were not increased in patients who had not received vincristine. Some striking case reports (18,19) have described myocardial infarction occurring in close temporal proximity to vincristine therapy, but there are no published data, to our knowledge, on the long-term risk of myocardial infarction after vincristine therapy. Vincristine has been associated with autonomic cardioneuropathy (8), and this association distinguishes it from vinblastine, for which raised myocardial infarction mortality risk was not seen in our data.

Overall, our data suggest, but do not give conclusive evidence, that treatment with vincristine may increase the long-term risk of death from myocardial infarction. The findings point to the need to re-examine the relationship between vincristine and myocardial infarction mortality in other cohorts and for a more detailed examination of this relationship, which we plan to do by a nested case–control study.

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Notes

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