Brief report

Malignant mesothelioma after radiation treatment for Hodgkin lymphoma

*Marie L. De Bruin,[1] *Jacobus A. Burgers,[2] Paul Baas,[2] Mars B. van 't Veer,[3] Evert M. Noordijk,[4] Marieke W. J. Louwman,[5] Josée M. Zijlstra,[6] Hendrik van den Berg,[7] Berthe M. P. Aleman,[8] and Flora E. van Leeuwen[1]

Departments of [1]Epidemiology and [2]Thoracic Oncology, The Netherlands Cancer Institute, Amsterdam; [3]Department of Hematology, Erasmus MC, Daniel den Hoed Cancer Center, Rotterdam; [4]Department of Radiotherapy, Leiden University Medical Center, Leiden; [5]Eindhoven Cancer Registry, Comprehensive Cancer Center South, Eindhoven; [6]Department of Hematology, Free University Medical Center, Amsterdam; [7]Department of Paediatric Oncology, Emma Children's Hospital/Academic Medical Center, University of Amsterdam, Amsterdam; and [8]Department of Radiotherapy, The Netherlands Cancer Institute, Amsterdam, The Netherlands

Malignant mesothelioma is a relatively uncommon malignancy. Although the pathogenesis is primarily related to asbestos, the disease may be associated with radiation exposure. Recently, increased risks for second primary mesothelioma after radiation for lymphoma have been reported. Because these findings are based on small numbers of patients, they need to be confirmed. We examined mesothelioma risk in 2567 5-year survivors of Hodgkin lymphoma. The risk was almost 30-fold increased in Hodgkin lymphoma patients treated with irradiation compared with the general population. Although histology and survival of the mesothelioma cases were comparable with cases from the general population, asbestos exposure and the proportion of males were lower than expected. The evidence for radiotherapy as cause for mesothelioma independent of exposure to asbestos is expanding, and the diagnosis of mesothelioma should be kept in mind whenever related symptoms arise in patients who had previous irradiation. (Blood. 2009;113:3679-3681)

Introduction

Malignant mesothelioma is a relatively uncommon malignancy. The pathogenesis is primarily related to asbestos, typically with a lag time of 10 to 40 years between exposure to asbestos and time of diagnosis.[1] In approximately 15% of mesothelioma patients, no overt exposure to asbestos can be identified,[2] and the disease may be related to other causes, such as irradiation, man-made mineral fibers, organic chemicals, viruses, and chronic inflammation.[3,4]

Recently, several epidemiologic studies have reported increased risk of second primary mesothelioma after treatment for testicular cancer[5] and lymphoma.[6-8] However, absolute numbers of reported mesothelioma cases were small, leaving the need for confirmation of the previous results and description of additional features. We therefore assessed the long-term risk of malignant mesothelioma in a cohort of 2567 patients treated for Hodgkin lymphoma (HL) in The Netherlands.

Methods

We performed a cohort study in all patients who had been treated for HL at 5 cancer centers/university hospitals in The Netherlands (The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital in Amsterdam, Erasmus MC/Daniel den Hoed Kliniek in Rotterdam, VU Medical Center in Amsterdam, Leiden University Medical Center in Leiden, and the Emma Children's Hospital/Academic Medical Center in Amsterdam) and in the affiliated hospitals of the Eindhoven Cancer Registry. Patient selection and methods of data collection have been described in detail previously.[9-12] Patients were younger than 51 years of age at the time of treatment for HL (1965-1995) with radiotherapy and/or chemotherapy and survived at least 5 years.

Follow-up started 5 years after first treatment for HL and ended at the date of diagnosis of mesothelioma, date of death, or date of most recent medical information on second malignancies, whichever came first. Follow-up was complete for 94% of the cohort. Mesothelioma was defined as a malignant tumor of the pleura (code C38.4) of malignant mesothelial morphology (code 9050/3, 9051/3, 9052/3, or 9054/3) according to the *International Classification of Diseases for Oncology*, 3rd Ed.[13] Pathology of all our cases had been reviewed by the national pathology expert panel, which had verified all diagnoses by directly reexamining the original biopsies on which the diagnosis of mesothelioma had been made. Medical records were screened, and general practitioners were contacted to identify previous exposure to asbestos. Radiotherapy charts were reviewed to assess whether the mesothelioma had developed in the radiation field; in addition, the radiation dose was recorded.

We compared the incidence of mesothelioma in our cohort with the general population, using incidence rates from the Eindhoven Cancer Registry[14] up to 1988 and from The Netherlands Cancer Registry[15] for the period 1989 to 2003. We calculated standardized incidence ratios (SIRs) and absolute excess rates, taking into account person-years of the patients in the HL cohort, according to methods previously described.[11]

Results and conclusions

After a median follow-up of 18.1 years, 8 men and 5 women of the 2567 patients experienced mesothelioma at least 5 years after being treated for HL. General characteristics of the study population are given in Table 1. Median age of the cohort members at first treatment for HL was 27.4 years, with a range of 3 to 50 years. Median time from treatment for HL to mesothelioma was 27.7 years, which was diagnosed at a median age of 56.4 years (Table 2). We found that 5-year survivors of HL experience an almost 26-fold increased risk for mesothelioma

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*M.L.D.B. and J.A.B. contributed equally to this study.

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Table 1. Characteristics of HL cohort, SIR, and AER of mesothelioma after HL

Characteristic	No. (%) of patients	Observed MM	Expected MM	SIR	(95% CI)	AER	(95% CI)
Overall	2567 (100)	13	0.51	25.7	(13.7-44.0)	3.5	(1.8-6.1)
Sex							
Male	1437 (56)	8	0.45	17.9	(7.7-35.3)	3.9	(1.6-7.9)
Female	1130 (44)	5	0.06	85.2	(27.6-199)	3.0	(0.9-7.1)
Age at first treatment of HL							
Less than or equal to 30 y	1559 (60.7)	7	0.10	66.8	(26.9-138)	3.0	(1.1-6.2)
31-50 y	1008 (39.3)	6	0.40	15.0	(5.5-32.5)	4.4	(1.4-9.8)
Treatment category*							
Radiotherapy only	730 (28.5)	1	0.17	5.8	(0.2-32.1)	0.7	(−0.1 to 4.7)
Chemotherapy only	232 (9)	0	0.06	—		—	
Radiotherapy + chemotherapy	1605 (62.5)	12	0.27	44.8	(23.2-78.3)	5.6	(2.8-9.9)
Radiotherapy ± chemotherapy†	2335 (91)	13	0.44	29.5	(15.7-50.4)	3.9	(2.0-6.7)
Follow-up							
5-25 y	2287 (89.1)	8	0.39	15.5	(5.7-33.8)	1.7	(0.6-3.9)
More than or equal to 25 y	280 (10.9)	5	0.12	58.4	(23.5-120)	21.5	(8.4-44.7)

SIR indicates standardized incidence ratio; AER, absolute excess rate; CI, confidence interval; and HL, Hodgkin lymphoma.
*Including primary/salvage treatment for HL and treatment for second malignancies other than mesothelioma.
†Indicates radiotherapy with or without chemotherapy.

compared with the general population (SIR, 25.7; range, 13.7-44.0, Table 1). The absolute excess number of mesothelioma was 3.5 cases per 10 000 patients per year. The risk of mesothelioma was much more pronounced among women (SIR, 85.2; range, 27.6-199) compared with men (SIR, 17.9; range, 7.7-35.3), among patients treated at young ages (age at first treatment < 31 years), and after prolonged follow-up (> 25 years after treatment). Among patients treated with radiotherapy, the risk was almost 30-fold increased (SIR, 29.4; range, 15.7-50.4). Although none of the 232 patients treated with chemotherapy only developed mesothelioma, the SIR for mesothelioma among patients treated with a combination of radiotherapy and chemotherapy was much higher (SIR, 44.8; range, 23.2-78.3) compared with patients treated with radiotherapy alone (SIR, 5.8; range, 0.2-32.1). This suggests a potential synergistic effect between chemotherapy and radiotherapy. High cumulative doses of alkylating chemotherapy have been linked previously to an increased risk lung cancer among HL patients.[16,17]

Diagnoses of all 13 cases were confirmed by the national pathology expert panel. The epithelial type was most prevalent (Table 2). Twelve tumors developed within the radiation field. In 3 patients, mesothelioma was their third primary tumor. All 13 mesothelioma patients were primarily treated in the 2 hospitals where HL patients from the highly industrialized areas were treated (The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital; Erasmus MC/Daniel den Hoed Kliniek). In the other hospitals, no mesothelioma cases were identified, although with a relative risk of 26 for mesothelioma among HL patients, we would have expected to observe 4 cases in these hospitals.

In this patient population, the characteristics of the mesotheliomas were similar to those seen after overt asbestos exposure. The majority had an epithelial subtype, and survival was limited (median, 10.2 months). However, our cases do not represent the general population of mesothelioma patients. Compared with all cases of mesothelioma newly diagnosed between 1989 and 2005 in The Netherlands,[15] our cases were younger (69% vs 23% younger than 60 years old) and more often female (38% vs 13%). In addition, exposure to asbestos was established in fewer patients than the expected 85%.[2] Our data on asbestos exposure revealed that only 7 of the 13 patients had previous exposure to asbestos (6 occupational, 1 environmental). Because we assume that less than 50% of the Dutch inhabitants have been exposed to asbestos, the exposure among our mesothelioma cases is higher than expected in the general population.[18] This might add to the scarce preclinical evidence for the synergistic action of asbestos and radiation in the pathogenesis of mesotheliomas.[19,20]

Table 2. Characteristics of patients with malignant mesothelioma after treatment for HL

Patient no.	Sex	Age at HL treatment, y	Treatment for HL	RT dose, cGy	HL to MM, y	Localization of MM	Age at MM, y	Histology of MM	Asbestos exposure*	Survival, mo
1	M	24.9	Thoracic and abdominal RT + CT	40	27.9	Right pleura	52.8	Epithelial	Occupational	20.5
2	M	33.1	Abdominal RT + CT	35‡	10.5	Right pleura	43.6	Epithelial	No	4.4
3†	M	22.1	Thoracic RT + CT	25	18.9	Right pleura	40.9	Epithelial	Occupational	21.9
4	F	33.2	Thoracic RT + CT	40	32.9	Left pleura	66.2	Mixed	No	10.2
5†	F	15.4	Thoracic RT	40	33.9	Right pleura	49.3	Epithelial	No	10.7
6†	F	21.8	Thoracic and abdominal RT + CT	40	18.2	Left pleura	40.0	Epithelial	No	7.3
7	M	24.8	Thoracic and abdominal RT + CT	30	31.7	Left pleura	56.4	Epithelial	Occupational	25.1
8	M	25.6	Thoracic and abdominal RT + CT	40	32.5	Right pleura	58.1	Epithelial	Environmental	5.3
9	M	37.5	Thoracic RT + CT	40	25.0	Left pleura	62.5	Epithelial	Occupational	5.2
10	M	42.5	Thoracic and abdominal RT	40	19.7	Left pleura	62.2	Epithelial	Occupational	5.9
11	M	38.7	Thoracic and abdominal RT + CT	40	19.5	Right pleura	58.2	Epithelial	Occupational	15.7
12	F	31.8	Thoracic and abdominal RT + CT	40	34.1	Left pleura	65.9	Epithelial	No	17.7
13	F	22.1	Thoracic RT + CT	40	27.7	Left pleura	49.8	Epithelial	No	1.7

HL indicates Hodgkin lymphoma; M, male; F, female; RT, radiotherapy; MM, malignant mesothelioma; and CT, chemotherapy.
*In The Netherlands, there is no exposure to endemic asbestos.
†Patient who developed another second primary malignancy after HL. Patient 3 had thoracic sarcoma treated with surgery 17 years after HL; patient 5 had breast carcinoma treated with chemotherapy 20 years after HL; and patient 6 had thyroid carcinoma treated with iodine 8 years after HL.
‡Patient was not irradiated to the chest.

Patients treated with radiation for HL (especially in combination with chemotherapy) experience a dramatically increased risk for mesothelioma, which manifests particularly 25 years or more after treatment. Our study confirms the high risks previously reported among other groups of patients treated with high-dose radiation to the chest.[6-8] Furthermore, our results suggest a potential interaction with chemotherapy or asbestos.

In conclusion, the evidence for radiotherapy as cause for mesothelioma independent of exposure to asbestos is expanding, but the absolute number of patients who are involved is low. Nevertheless, the diagnosis of mesothelioma should be kept in mind whenever new symptoms arise in patients who had previous irradiation.

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Authorship

Contribution: M.L.D.B., J.A.B., B.M.P.A., and F.E.v.L. contributed to the design of the study, were involved with the data analysis and interpretation, and contributed to the writing of the report; and P.B., M.B.v.V., E.M.N., M.W.J.L, J.M.Z., and H.v.d.B. contributed patients to the cohort and revised the manuscript. All authors approved the final manuscript.

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Correspondence: Jacobus A. Burgers, Department of Thoracic Oncology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands; e-mail: s.burgers@nki.nl.

References

1. Zucali PA, Giaccone G. Biology and management of malignant pleural mesothelioma. Eur J Cancer. 2006;42:2706-2714.
2. Huncharek M. Non-asbestos related diffuse malignant mesothelioma. Tumori. 2002;88:1-9.
3. Cavazza A, Travis LB, Travis WD, et al. Post-irradiation malignant mesothelioma. Cancer. 1996; 77:1379-1385.
4. Warren S, Brown CE, Chute RN, Federman M. Mesothelioma relative to asbestos, radiation, and methylcholanthrene. Arch Pathol Lab Med. 1981; 105:305-312.
5. Travis LB, Fossa SD, Schonfeld SJ, et al. Second cancers among 40 576 testicular cancer patients: focus on long-term survivors. J Natl Cancer Inst. 2005;97:1354-1365.
6. Hodgson DC, Gilbert ES, Dores GM, et al. Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma. J Clin Oncol. 2007;25: 1489-1497.
7. Teta MJ, Lau E, Sceurman BK, Wagner ME. Therapeutic radiation for lymphoma: risk of malignant mesothelioma. Cancer. 2007;109:1432-1438.
8. Tward JD, Wendland MM, Shrieve DC, Szabo A, Gaffney DK. The risk of secondary malignancies over 30 years after the treatment of non-Hodgkin lymphoma. Cancer. 2006;107:108-115.
9. Aleman BM, van den Belt-Dusebout AW, Klokman WJ, et al. Long-term cause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol. 2003;21:3431-3439.
10. van Leeuwen FE, Klokman WJ, Hagenbeek A, et al. Second cancer risk following Hodgkin's disease: a 20-year follow-up study. J Clin Oncol. 1994;12:312-325.
11. van Leeuwen FE, Klokman WJ, Veer MB, et al. Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. J Clin Oncol. 2000;18:487-497.
12. Aleman BM, van den Belt-Dusebout AW, De Bruin ML, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood. 2007;109:1878-1886.
13. World Health Organization. International Classification of Diseases for Oncology, 3rd Ed. Geneva, Switzerland: World Health Organization; 2000.
14. Janssen-Heijnen ML, Damhuis RA, Klinkhamer PJ, Schipper RM, Coebergh JW. Increased but low incidence and poor survival of malignant mesothelioma in the southeastern part of The Netherlands since 1970: a population-based study. Eur J Cancer Prev. 1999;8:311-314.
15. Netherlands Cancer Registry. Cancer in figures: Association of Comprehensive Cancer Centres. http://www.ikcnet.nl. Accessed October 1, 2008.
16. Travis LB, Gospodarowicz M, Curtis RE, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J. Natl Cancer Inst. 2002;94:182-192.
17. van Leeuwen FE, Klokman WJ, Stovall M, et al. Roles of radiotherapy and smoking in lung cancer following Hodgkin's disease. J Natl Cancer Inst. 1995;87:1530-1537.
18. Peterson JT Jr, Greenberg SD, Buffler PA. Non-asbestos-related malignant mesothelioma: a review. Cancer. 1984;54:951-960.
19. Altomare DA, Vaslet CA, Skele KL, et al. A mouse model recapitulating molecular features of human mesothelioma. Cancer Res. 2005;65:8090-8095.
20. Hei TK, Geard CR, Osmak RS, Travisano M. Correlation of in vitro genotoxicity and oncogenicity induced by radiation and asbestos fibres. Br J Cancer. 1985;52:591-597.