Haematologica 1998; 83:636-644 original paper

The risk of non-Hodgkin's lymphoma after Hodgkin's disease, with special reference to splenic treatment

Riccardo Maurizi Enrici,° Anna Paola Anselmo,# Valter Iacari,° Mattia Falchetto Osti,° Mariaquila Santoro,° Vincenzo Tombolini,* Franco Mandelli,# Carissimo Biagini°

°Chair of Radiation Oncology, Department of Radiation Oncology, Institute of Radiology, Policlinico Umberto I, "La Sapienza" University of Rome; #Department of Human Biopathology, Hematology Section, "La Sapienza" University of Rome; *Chair of Radiation Oncology, Hospital "S. Maria di Collemaggio", University of L'Aquila, Italy

Abstract

Background and Objective. **One of the consequences of the enormous improvement in survival rates of patients treated for Hodgkin's disease (HD) is the emergence in the long term of treatment-related complications, particularly secondary cancers. This study was undertaken to observe the occurrence of non-Hodgkin's lymphoma (NHL) in patients treated for HD and to identify the etiological role of various risk factors, especially spleen irradiation, in the pathogenesis of this illness.**

Design and Methods. **From 1972 to 1996, the Department of Radiation Oncology and the Hematology Section of "La Sapienza" University of Rome observed and analyzed the occurrence of NHL in 1,391 patients treated for HD. The average follow-up period was 84 months. For a more accurate calculation of the risk of the occurrence of NHL, the patients were first divided into 3 groups according to their initial treatment and also according to the total treatment they had received. Then, in order to establish the possible connection between NHL and splenic treatment the patients were also divided into 3 subgroups according to whether they had undergone splenectomy, splenic irradiation or neither of these. Two different methods of statistical analysis were used: (a) the cumulative risk (confidence interval) was evaluated in relation to treatment (initial and at the time of salvage) and (b) the Cox model was applied to identify the variables which play a role in the appearance of NHL. The cumulative risk of developing NHL was assessed using the Kaplan and Meier method. A multivariate analysis was performed using the Cox Proportional Hazard Model.**

Results. **A total of 20 cases of NHL were observed, appearing between 17 and 206 months after initial treatment. The cumulative risk was 0.8%, 1.8%, 2.6% and 3.5% at 5, 10, 15 and 20 years respectively. According to the multivariate analysis, significant risk factors were splenic irradiation and age (> 40 years). Splenic irradiation (vs no splenectomy/no splenic irradiation) showed a relative risk of 5.69, p = 0.0280, while age over 40 showed a relative risk of 3.05, p = 0.0152.**

Interpretation and Conclusions. **From the results of this study, it appears that there is a possibility that splenic irradiation and age over 40 increase the risk of NHL in HD patients. Further studies are needed to investigate in greater depth the role of spleen irradiation in the occurrence of this illness.**

Correspondence: Prof. Riccardo Maurizi Enrici, Chair of Radiation Oncology, Department of Radiation Oncology, Institute of Radiology, Policlinico Umberto I, "La Sapienza" University of Rome, viale Regina Elena 432, 00161 Rome, Italy.
Phone: international +39-06-49970456/491774 • Fax: international +39-06-49970456/491774.

Key words: Hodgkin's disease, non-Hodgkin's lymphoma, spleen irradiation, radiotherapy, chemotherapy

Hodgkin's disease (HD) is currently one of the most curable cancers. New developments in radiotherapy (RT) and in chemotherapy (CT) help improve the overall survival and cure rates of patients HD. However, together with these encouraging results, it has also been observed that patients treated for HD have with time suffered from complications related to the treatment they have received. As survival times increase, late complications of enormous clinical importance are emerging, including cardiovascular,[1] pulmonary, gonadal and thyroid dysfunction,[2] immunity alterations and the appearance of a second tumor,[3-5] particularly acute non-lymphoid leukemia (ANLL),[6,7] non-Hodgkin's lymphoma (NHL)[8] and solid tumors (ST).[9] The increase in the risk of ANLL has been associated with host-related factors and the type of treatment undergone.[10] Several authors report that the risk is higher in patients treated with combined RT and CT including mechlorethamine and procarbazine.[11-13] The risk of ST has been related to treatment with RT alone or in combination with CT.[14,15] The most frequent ST are lung cancer, breast cancer, skin melanoma, gastrointestinal cancer and sarcoma of the bone.

The appearance of NHL in patients treated for HD is somewhat rare and the pathogenesis is still not clear. In the papers published over the last few years regarding the occurrence of NHL, the rate of incidence ranges from 0.7%[16]-5.9%.[17] The majority of secondary NHL have been intermediate- or high-grade lymphomas of the B-cell immunophenotype. For some authors,[8,17] the occurrence of NHL is related to radiochemotherapy treatment; the risk is concentrated in the first year following the start of treatment, declines in the subsequent 5 years, and then

rises to a peak in the 10-14 year observation period.[18] On the other hand, other authors[14,15,19] report the absence of any link between treatment received, age and the appearance of NHL. Zarate-Osorno *et al*.[19] offer the hypothesis that the occurrence of B-cell NHL may be caused by histologic progression of HD, while Bennett *et al*.[16] report a significant increase in the risk of NHL in patients with the histologic subtype of HD characterized by lymphocytic predominance. In this report, we analyze a cohort of 1,391 patients with HD. The aim was to assess the risk associated with splenic treatment, RT, CT and other factors in the development of NHL.

Materials and Methods

Patient population

This study was conducted from 1972 to 1996 on a cohort of 1,391 patients treated in the Department of Radiation Oncology and the Hematology Department of "La Sapienza" University of Rome.

The diagnosis of HD was made using the Rye classification and the patients were staged according to the Ann-Arbor classification.

For 499 (35%) of the patients the follow-up period was longer than 10 years and for 810 patients (58%), it continued until December 1, 1996. Seventy-three (5%) patients had been lost to follow-up as at December 1, 1996. For all the patients in this study, the computer data base included: date of birth, sex, age at diagnosis of HD, histology, clinical and/or pathologic stages, clinical trial protocols, date on which splenectomy had been performed, date and type of initial treatment, results of initial treatment, progression and/or relapse, date and type of treatment of progression and/or relapse, results of treatment for progression and/or relapse, date of last known vital status or diagnosis of NHL or death. On diagnosis of NHL, the histologic slides of both HD and secondary NHL were reviewed by an experienced hematopathologist to exclude the possibility of any error in the initial diagnosis. As a results, four patients with secondary NHL had to be excluded from this analysis, in two cases because the original HD was rediagnosed as a primary NHL, in one case because the histologic slides were not available, and in another case because the slides were reviewed by two different hematopathologists who differed in their diagnoses of the secondary illness. The radiological records were re-examined to establish whether NHL occurred inside or outside previously irradiated fields. NHL occurring in a previously irradiated field was observed as developing inside or at the margins of the zone. Table 1 shows the clinical characteristics of the 1,391 patients.

Treatment

Before 1976, the patients were not included in standardized treatment protocols. However, the cases have always been discussed every week by radiotherapists and hematologists, as still happens in the most interesting cases and relapses. Between 1976 and 1996, the patients were included in three successive clinical protocols (ROMA HD 76, ROMA HD 83 and ROMA HD 94).

In order to obtain a more accurate calculation of the risk of occurrence of NHL and the connection with the type of treatment received, five different analyses were carried out, with different sets of criteria.

For the first analysis the patients were divided into 3 groups according to their initial treatment:

1. four hundred and thirty-nine (31.6%) patients were treated with radiotherapy alone; of these, 143 (32.6%) received sub-total nodal irradiation, 47 (10.7%) total nodal irradiation, 85 (19.4%) mantle-field, 16 (3.6%) inverted Y, 6

Table 1. Clinical characteristics of patients with Hodgkin's disease.

Characteristics	*No. of patients*	*%*
All patients	1391	100
Male	691	49.7
Female	700	50.3
Stage		
I	159	11.4
II	653	47
III	383	27.5
IV	196	14.1
Age		
< 25	415	29.8
25-40	592	42.6
> 40	384	27.6
Histology		
Mixed cellularity	479	34.4
Nodular sclerosis	673	48.4
Lymphocytic predominance	105	7.6
Lymphocytic depletion	89	6.4
Unclassified	45	3.2
Initial treatment		
*Radiotherapy alone**	439	31.6
Chemotherapy alone	291	20.9
Radiotherapy plus chemotherapy	661	47.5
Total treatment		
Radiotherapy alone	352	25.3
Chemotherapy alone	252	18.1
Radiotherapy plus chemotherapy	787	56.6
Splenic treatment		
Splenectomy	634	45.6
Splenic irradiation	335	24
(=40 Gy)	(163)	(11.7)
(<40 Gy)	(172)	(12.3)
No splenectomy/no splenic irradiation	422	30.4
Average follow-up (in months)	84	

**142 patients received one adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) course.*

(1.4%) involved field, 121 (27.5%) sub-total nodal irradiation + one adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) course, 21 (4.8%) total nodal irradiation + one ABVD course;
2. two hundred and ninety-one (20.9%) patients received chemotherapy alone; of these, 136 (46.4%) were given 6 mechlorethamine, vincristine, procarbazine and prednisone (MOPP) courses, 60 (20.8%) were given 6 ABVD courses, 64 (21.8%) received 8 alternating MOPP/ABVD courses, 29 (10%) were given 8 alternating vincristine, procarbazine, and prednisone (OPP)/ABVD courses and 2 (0.7%) other kinds of chemotherapy;
3. combined chemotherapy plus radiotherapy induction treatment was administered to 661 patients (47.5%). In this group, radiotherapy (35 Gy, total nodal irradiation) + MOPP (6 courses) was used in 86 (13%) cases; radiotherapy (35 Gy, total nodal irradiation) + ABVD (6 courses) in 89 (13.5%) cases; involved field radiotherapy and MOPP (≤ 3 courses) in 11 (1.7%) cases; involved field radiotherapy and ABVD (≤ 4 courses) in 166 (25.1%) cases; radiotherapy (20 Gy involved field irradiation) + MOPP/ABVD (8 courses) in 112 (16.9%) cases; radiotherapy (20 Gy involved field irradiation) + OPP/ABVD (8 courses) in 100 (15.1%) cases; radiotherapy (30 Gy sub-total nodal irradiation) + cyclophosphamide, vincristine, procarbazine, and prednisone (COPP)/ABVD (2 courses) in 36 (5.5%) cases; radiotherapy (30 Gy total nodal irradiation) + COPP/ABVD (2 courses) in 12 (1.8%) cases; radiotherapy (30 Gy, sub-total nodal irradiation) + COPP/adriamycin, bleomycin, and vinblastine (ABV)/ifosfamide, methotrexate, etoposide, and prednisone (IMEP) (2 courses) in 33 (5%) cases; radiotherapy (30 Gy, total nodal irradiation) + COPP/ABV/IMEP (2 courses) in 12 (1.8%) cases and involved field radiotherapy and other kinds of chemotherapy in 4 cases (0.6%).

For the second analysis, patients were divided according to their total treatment:
1. patients who received radiotherapy only: 352 (25.3%);
2. patients who received chemotherapy only: 252 (18.1%);
3. patients who received radiotherapy and chemotherapy: 787 (56.6%).

For the third analysis, the patients were divided into 2 groups according to whether they received subsequent treatment or not:
1. patients who received initial treatment only: 1,139 (81.9%);
2. patients who received subsequent treatment for relapse or progression: 252 (18.1%).

For the fourth analysis, the patients were divided into 2 groups according to whether they received splenic treatment (splenic irradiation or splenectomy) or not:
1. patients who underwent splenectomy or splenic irradiation: 969 (69.7%);
2. patients who underwent neither splenectomy nor splenic irradiation: 422 (30.3%).

For the fifth analysis, the patients were divided into 3 groups to establish the risk of cancer after splenic treatment:
1. patients who underwent splenectomy: 634 (45.6%);
2. patients who underwent splenic irradiation: 335 (24.1%);
3. patients who underwent neither splenectomy nor splenic irradiation: 422 (30.3%).

Data analysis

To establish the possible connection between NHL and treatment received, two different methods of analysis were used: (a) the cumulative risk (confidence interval) was assessed in relation to treatment (initial and at the time of relapse) and (b) the Cox model was applied to identify the variables which play a role in the appearance of NHL. The cumulative risk of developing NHL was assessed using the Kaplan and Meier method.[20] The risk period for NHL was calculated as starting from the date of diagnosis of HD and ending at the date of diagnosis of NHL, or last known vital status, or progression, or relapse, or death, or December 1, 1996, whichever came first. Relapsing or progressing patients were assessed at the date of relapse and were considered free of second primary cancer at that date. For patients with progression and/or relapse, the risk period for NHL was re-set as beginning at treatment for progression and/or relapse and ending at the date of diagnosis of NHL, or last known vital status, or death, or December 1, 1996, whichever came first.

The risk of occurrence of NHL was analyzed: (a) in all patients, in relation to treatment given at presentation, considered disease-free (relapsed patients, assessed at relapse, were considered disease-free until the onset of relapse) and (b) in all patients, in relation to the different treatment given to each patient at presentation (for patients who did not relapse) and, for relapsing or progressing patients, in relation to the sum of the different types of treatment given to each patient at presentation and, after relapse and/or progression, at salvage. A multivariate analysis was performed using the Cox Proportional Hazard Model;[21] for this analysis, we proposed the following variables as having a possible effect on the development of NHL:
1. age (<40 versus >40);
2. stage (I-II versus III-IV);
3. histology (lymphocytic predominance histologic subtype versus others, since lymphocytic predominance, has emerged as a risk factor in the occurrence of NHL in international literature);

Table 2. Characteristics of patients with non-Hodgkin's lymphoma (NHL).

Case no.	*Age**	*Sex*	*Histology*	*Stage*	*Splenic treatment*	*Treatment at onset of HD and relation of site of NHL to previously irradiated fields*	*Time elapsed since first therapy (in months)*	*Therapy for relapse*	*Type of NHL*	*PS*	*LDH*	*Immunologic phenotype*
1	51	M	LD	III A	Splenectomy	ABVD+STNI (outside)	122	MOPP	Intermediate grade	90	–	B-cell
2	53	F	LP	II B	–	ABVD+STNI (outside)	96	No relapse	High grade	100	–	B-cell
3	55	F	LP	I A	Splenectomy	STNI (outside)	101	Other CT	Intermediate grade	90	288	B-cell
4	33	F	MC	IV B	Splenic irradiation	OPP/ABVD+TNI (in field)	52	Other CT	High grade	30	184	T-cell
5	54	M	MC	I A	Splenectomy	TNI (outside)	98	No relapse	High grade	100	1658	B-cell ($CD20^+$)
6	30	F	NS	IV B	Splenic irradiation	OPP/ABVD+TNI (at margins)	33	No relapse	High grade	100	353	T-cell
7	39	F	NS	III A	–	COPP/ABVD+TNI (in field)	18	No relapse	High grade	100	169	T-cell ($CD30^+$,$CD15^-$, $CD20^-$, $CD45R0^-$)
8	49	M	NS	II A	Splenectomy	MOPP	29	RT IF (outside)	High grade	100	138	T-cell
9	51	F	NS	I A	Splenectomy	TNI (outside)	206	No relapse	High grade	100	–	B-cell
10	34	M	NS	II B	Splenic irradiation	ABVD/MOPP+RT IF (outside)	87	No relapse	Mycosis fungoides	90	–	T-cell
11	36	M	LP	II A	Splenic irradiation	ABVD+TNI (in field)	36	No relapse	High grade	100	233	B-cell ($CD20^+$)
12	39	M	MC	II A	Splenectomy	"Mantle"(outside)	35	MOPP	High grade	90	–	T-cell
13	59	M	MC	II B	Splenic irradiation	MOPP/ABVD+TNI (outside)	21	No relapse	High grade	100	840	B-cell
14	43	M	LP	II A	Splenic irradiation	ABVD+STNI (in field)	22	No relapse	High grade	100	460	B-cell
15	17	M	Unclassified	III B	Splenectomy	MOPP/ABVD+TNI (at margins)	159	No relapse	High grade	30	–	B-cell
16	36	F	NS	III B	Splenic irradiation	MOPP/ABVD+RT IF (in field)	17	No relapse	High grade	100	660	T-cell
17	22	M	MC	III A	Splenectomy	ABVD+TNI (in field)	41	No relapse	Low grade	90	149	B-cell ($L26^+$)
18	48	F	MC	III A	Splenectomy	MOPP/ABVD	29	No relapse	High grade	90	–	B-cell ($CD20^+$,$CD30^-$ $CD3^-$, EMA^-)
19	27	M	MC	III B	–	MOPP/ABVD	79	No relapse	High grade	100	247	T-cell
20	59	M	LD	II B	Splenectomy	MOPP	105	ABVD+"inverted Y"(outside)	High grade	100	–	B-cell

**Age at HD diagnosis; HD: Hodgkin's disease; PS: performance status; LDH: serum lactate dehydrogenase; LD: lymphocytic depletion; ABVD: adriamycin, bleomycin, vinblastine, and dacarbazine; STNI: sub-total nodal irradiation; MOPP: mechlorethamine, vincristine, procarbazine, and prednisone; LP: lymphocytic predominance; CT: chemotherapy; MC: mixed cellularity; OPP: vincristine, procarbazine, and prednisone; TNI: total nodal irradiation;NS: nodular sclerosis; COPP: cyclophosfamide, vincristine, procarbazine, and prednisone; RT IF: "involved field" radiotherapy.*

4. treatment groups (two independent variables: CT versus RT; RT plus CT compared to RT alone);
5. splenic treatment (first: splenic treatment versus no splenic treatment; second: splenectomy versus no splenectomy or splenic irradiation, splenic irradiation versus no splenic irradiation or splenectomy).

The time-dependent covariate analysis was applied for progressing and/or relapsing patients.

Data were analyzed using the programs in the SPSS software packages.[22]

Results

Among the 1,391 patients with an average follow-up of 84 months (maximum follow-up time: 361 months), 20 cases of NHL developed between 17 and 206 months (average: 53.5 months) after initial treatment. Table 2 shows the clinical characteristics of the 20 patients. The average age at the time of diagnosis was 41 years (range: 17-59 years). Of the 20 cases, 12 were male and 8 female. Fourteen of the cases occurred in patients who did not relapse and 6 occurred after a relapse. Seven lymphomas developed within a previously irradiated field, 12 outside and 2 at the margins. Ten of the lymphomas appeared in splenectomized patients, 7 in patients whose spleen was irradiated and 3 in patients who did not undergo any splenic treatment.

Risk of occurrence of NHL: cumulative risk in general and in relation to splenic treatment

The increased risk of NHL, irrespective of treatment, was 1.8% (0.90-0.2) and 3.5% (1.3-5.7) after 10 and 20 years respectively. In the univariate analysis, the cumulative risk of NHL after splenectomy was 0.3% (0-0.8) at 5 years and 3.7% (0.8-6.6) at 20 years; for patients whose spleen was irradiated the cumulative risk was 3.2% (0.8-5.7) at 5, 10, 15, and 20 years. In patients not subjected to splenic treatment the risk was 0.2% (0-0.8) at 5 years and 1.4% (0-3.1) at 20 years (Table 3) (p= 0.019). The results of the second division of patients (splenectomy or splenic irradiation vs no splenectomy and no splenic irradiation) showed no statistically significant differences between the two groups.

Risk of occurrence of NHL: cumulative risk in relation to initial and total treatment

The relation of initial therapy (i.e. radiotherapy alone, chemotherapy alone and combined methods without treatment for recurrence) to the occurrence of NHL was assessed.

First: the cumulative risk of NHL according to the type of treatment received is shown in Table 4. The highest risk of NHL was found in the radiotherapy group and the cumulative risk increased after 20 years of observation (p = 0.654).

Second: the cumulative probability of developing NHL can be related to the sum of the different types of treatment given to each patient at presentation and, in case of relapse, at salvage. The highest risk of NHL was observed in patients treated with CT plus RT or RT alone (cumulative risk= 3.8%), while in the group of patients treated with CT alone the risk was 1.6%. No substantial differences were observed between initial and salvage types of treatment.

Third: the univariate analysis shows no statistical differences (p = 0.708) between patients who received additional treatment for relapse or progression and the patients who received initial treatment only.

Risk of occurrence of NHL: multivariate analysis

Table 5 shows the results of the Cox Model analysis of the effects of different types of treatment and of various clinical characteristics in the occurrence of NHL. According to the multivariate analysis, significant risk factors are splenic irradiation and age. In fact, splenic irradiation vs no splenectomy and no splenic irradiation shows a relative risk of 5.69, p= 0.0280, while splenectomy vs no splenectomy and no splenic irradiation shows a relative risk of 1.65, p= 0.4635. Moreover, age >40 years shows a relative risk of 3.05, p = 0.0152.

Discussion

The occurrence of NHL is one of the most serious long-term complications of modern treatment of

Table 3. Cumulative risk (confidence interval) and frequency of non-Hodgkin's lymphoma (NHL) in relation to splenic treatment.

		Cumulative risk % (CI)				
	N° NHL/N° patients	*5 years*	*10 years*	*15 years*	*20 years*	*p*
Splenectomy	10/634	0.3 (0-0.8)	1.3 (0.2-2.4)	2.4 (0.7-4.1)	3.7 (0.8-6.6)	
Splenic irradiation	7/335	3.2 (0.8-5.7)	3.2 (0.8-5.7)	3.2 (0.8-5.7)	3.2 (0.8-5.7)	0.019
No splenectomy/no splenic irradiation	3/422	0.2 (0-0.8)	1.4 (0-3.1)	1.4 (0-3.1)	1.4 (0-3.1)	
All patients	20/1391	0.8 (0.3-1.4)	1.8 (0.9-2.7)	2.6 (1.3-3.9)	3.5 (1.3-5.7)	

Table 4. Cumulative risk (confidence interval) and frequency of non-Hodgkin's lymphoma in relation to treatment.

	No. of non-Hodgkin's lymphoma/ no. of patients	Cumulative risk % (CI) 5 years	10 years	15 years	20 years	p value
Initial treatment						
Radiotherapy	6/439	0.7 (0-1.5)	1.5 (0.1-2.9)	1.5 (0.1-2.9)	3.4 (0-43.2)	
Chemotherapy	4/291	0.4 (0-1.3)	1.8 (0-3.9)	3.1 (0-6.4)	3.1 (0-6.4)	0.65
Radiotherapy plus chemotherapy	10/661	0.7 (0-1.5)	2.1 (0.5-3.7)	3.4 (1-5.8)	3.4 (1-5.8)	
Total treatment						
Radiotherapy	5/352	0.9 (0-2)	1.4 (0-2.9)	1.4 (0-2.9)	3.8 (0-8.5)	
Chemotherapy	2/252	0	1.6 (0-3.8)	1.6 (0-3.8)	1.6 (0-3.8)	0.49
Radiotherapy plus chemotherapy	13/787	1.1 (0.2-1.9)	2.1 (0.7-3.5)	3.8 (1.4-6.2)	3.8 (1.4-6.2)	
Initial treatment only	15/1139	0.8 (0.2-1.4)	1.6 (0.6-2.6)	2.2 (1-3.5)	3.4 (0.8-6)	0.70
All treatments	5/252	0.9 (0-2.1)	2.2 (0-4.5)	3.8 (0-7.5)	3.8 (0-7.5)	

Table 5. Cox proportional hazard model of risk factors in the development of non-Hodgkin's lymphoma.

Variables	*Coefficient*	*Standard error*	*Relative risk*	*p value*
Age				
<40 versus >40	1.11	0.46	3.05	0.0152
Stage				
I-II versus III-IV	0.04	0.52	1.04	0.9389
Histology				
Lymphocytic predominance versus others	-0.88	0.58	0.42	0.1331
Total treatment				
Chemotherapy versus radiotherapy	0.52	0.75	1.68	0.4869
Radiotherapy plus chemotherapy versus radiotherapy	0.16	0.66	1.17	0.8087
Splenic treatment				
Splenectomy versus no splenectomy or no splenic irradiation	0.50	0.68	1.65	0.4635
Splenic irradiation versus no splenic irradiation or no splenectomy	1.74	0.79	5.69	0.0280

HD.[8,16,19] In this study, we have focused on observing the appearance of NHL in relation to splenic treatment and have found, for the first time in literature, a high risk of NHL after splenic irradiation. Several studies report splenectomy and splenic irradiation as potential risk factors in the occurrence of ANLL.[23-26] In contrast, the appearance of NHL after the diagnosis of HD has been reported to be linked to combined therapy[8,17] and is concentrated in the first years of follow-up. Regarding splenic irradiation, Daley *et al.*[27] demonstrate that all splenic structures can show numerous changes due to radiation: the irradiated spleen tends to be small, with the capsule thickened by collagen deposits, associated with severe diffuse fibrosis of the red pulp. The most significant alteration is the myointimal proliferation of arteries. Although none of these pathologic features is specific in itself, the presence of a combination of them is characteristic of radiation injury. Moreover, splenic atrophy after radiation treatment, estimated at approximately 30-40%, predisposes patients to fulminant pneumococcal sepsis and Waterhouse-Friderichsen syndrome.[28] Coleman *et al.*[29] showed that patients with HD or NHL who have had approximately 40 Gy for splenic irradiation have developed functional hyposplenia. In a recent report, Dietrich *et al.*[30] studied a series of 892 continuously disease-free adult patients with HD and analyzed the increase in the risk of second cancers, suggesting a connection between splenectomy or splenic irradiation and an increase in the risk of second primary cancer, not only acute non-lymphoid leukemia. The mechanism by which splenic hypofunction or the absence of the spleen may involve the occurrence of secondary can-

cer has not been established.[25,30] Dietrich *et al.*[30] stated that no experimental data regarding the potential role of the spleen in tumoral immunosurveillance is available. Moreover, if the initial triggering of the cell-mediated immune response takes place in the spleen and the lymph nodes, it could be thought that the immunodysfunction following splenic treatment may considerably increase the damage of tumoral immunosurveillance capabilities. There is controversy regarding the role of splenectomy. Van Leeuwen *et al*.[26] have reported that splenectomy might predispose to secondary ANLL, not to NHL, in agreement with Van der Velden *et al.*[31], Zinzani *et al.*[32] and Kaldor *et al.*[13] In a recent study on 6,315 persons who underwent splenectomy because of traumatic rupture of the spleen, hematologic disorders, or for facilitating surgery on contiguous organs, Mellemkjoer *et al.*[33] reported no increased risk of second primary cancers among the patients who underwent splenectomy because of traumatic rupture of the spleen (patients were followed up for 13 years). An increased number of second primary cancers did, however, occur in patients who underwent splenectomy for non-traumatic reasons (malignant and non-malignant disease). In fact, after traumatic rupture, splenic cells spill onto the peritoneal surfaces and determine partial return of the splenic function.[34] Immunodeficiency is peculiar to HD[35,36] and, as spleen irradiation induces functional hyposplenia, it is conceivable that the immune defect of chronic T-cells[37] may permit a clonal proliferation of B-cells,[38] and may increase the immunosuppression of HD itself. In fact, NHL is one of the most frequent tumors observed in individuals with altered immune states or immunosuppression due to organ transplant, genetic or congenital causes or as a consequence of HIV.[39,40]

A recent study on 3,033 patients with HD by Bennett *et al.*[16] in which 22 cases of NHL were observed, seems to suggest that the histologic subtype characterized by lymphocytic predominance shows a higher NHL risk rate (3.8% incidence, whereas for the nodular sclerosis subtype and mixed cellularity it was 0.7% and 0.3% respectively); results from other studies,[25,41-44] agree with these conclusions. In our series of patients, the incidence of NHL was 3.8% for the lymphocytic predominance histologic subtype, while it was 1.4% for mixed cellularity, 2.2% for lymphocytic depletion and 0.7% for nodular sclerosis. Furthermore, Bennett *et al*.[16] stated that in the case of large B-cell lymphomas, the occurrence of NHL may be caused by a histologic process and that there is no connection with the treatment received. The same study also reported that if NHL with large B-cells occurs within 3 years after the end of initial therapy, and with T-cells after 5-6 years, other factors are responsible, probably the treatment received. In contrast, a recent study on 64 patients in the *Peter MacCallum Cancer Institute* (Melbourne, Australia)[45] showed no connection between the subtypes of HD and development of NHL. Moreover, Wickert *et al.*[46] have suggested that the occurrence of Large Cell Lymphoma of B-cells represents clonal progression of the lymphocytic predominance subtype of HD. This finding and others[47,48] would suggest that, at least in some cases, the Reed-Sternberg variant may be related to B-cell lymphoproliferative disorders. Zarate-Osorno *et al.*,[19] studying 14 patients who developed secondary NHL, agree with the hypothesis of a histologic process. They add that the occurrence of NHL outside a node, with an intermediate or high grade of B-cells, may suggest that immune deficiency is involved. As a matter of fact, the clinical, histologic and immunophenotypic features in patients with NHL were similar to those of individuals with immune deficiency.

In our study, the detailed analysis of the relation between splenic treatment and the occurrence of NHL shows points of particular interest. In the cases of NHL after splenic irradiation (7 cases), the highest risk is concentrated in the first five years after the end of therapy, whereas in patients who underwent splenectomy or received neither splenectomy nor splenic irradiation, the risk period increases to 20 years. One possible explanation is that the radiation injury to the spleen speeds up the histologic progression of the foci already present in the spleen, as well as increasing the immunologic impairment associated with the disease itself. After splenectomy, the conditions would not exist for this speeding-up process to take place.

In our experience, age was the variable with statistical significance ($p = 0.0152$). Age is the major risk factor for developing second cancers in the population with HD in the same way that age is a major risk factor for almost all cancers in the general population. It is difficult to compare the incidence of NHL in HD patients with the incidence of NHL in the general population because of the low overall number of cases of this illness.

It can be concluded that one of the greatest therapeutic successes over the past 30 years has been the extraordinary improvement in survival rates of patients with HD. This success, however, has a price: induced cancer. Patients treated with splenic irradiation have the highest risk of developing NHL. It is uncertain whether this is a biological phenomenon, whether it is related to the status of patients with HD, or whether it is an effect of treatment with RT or combined RT plus CT. It should also be observed that these results reflect treatment carried out 15 or 20 years ago, when higher CT doses were used and larger volumes of tissue were irradiated. It is important, therefore, to continue to study patients treated for HD and observe the occurrence of NHL after splenic treatment. Further studies are needed on patients who have received spleen irradiation, in order to confirm the results of our study.

The aim is to maintain the same excellent results in

terms of overall survival in patients with HD and at same time ensure freedom from relapse and from any other complications.[3,49]

Contributions and Acknowledgments

RME was responsible for the conception of the study, its design, ethical approval, funding, direct supervision, recruitment, day-to-day contact with participants, data handling, and interpretation. APA was responsible for randomization, biochemical measurements, and following the patients clinically. VI was responsible for statistical analysis. MFO contributed to the execution of the study. MS was responsible for the design of the study and the writing of the paper. VT contributed to the execution of the study. FM was responsible for the organization of the group. CB was responsible for the organization of the group.

The first author has dedicated his life's work to studying Hodgkin's disease and treatment-related complications, and was responsible for the conception of the study. The 2nd, 3rd, 4th, 5th and 6th authors are listed in alphabetical order. The 7th and 8th authors played a supervisory role over the working group.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

Manuscript received February 3, 1998; accepted April 8, 1998.

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