Secondary malignancies after treatment for indolent non-Hodgkin's lymphoma: a 16-year follow-up study

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ABSTRACT

Background
Relatively little information is available on the incidence of secondary cancer in non-Hodgkin's lymphoma. The aim of this long-term follow-up study was to determine the incidence, the time free of second tumors, and risk factors for developing secondary cancer in a homogeneous group of patients with non-Hodgkin's lymphoma.

Design and Methods
We evaluated a total of 563 patients with indolent non-Hodgkin's lymphoma enrolled in *Gruppo Italiano Studio Linfomi* trials from 1988 to 2003.

Results
After a median follow-up of 62 months, 39 patients (6.9%) developed secondary cancer: 12 myelodysplastic syndromes/acute myeloid leukemia, and 27 solid tumors. The overall standardized incidence ratio of secondary malignancy in patients with non-Hodgkin's lymphoma was higher than the risk of malignancy in the general population. The standardized incidence ratio was elevated in male patients and in patients under 65 years old at first treatment. Overall, the cumulative incidence of secondary cancer at 12 years was 10.5%, after correction in a competing-risk model. Univariate and multivariate Cox regression analyses showed that older age at the time of diagnosis, male sex, and fludarabine-containing therapy had significant negative impacts on the time free of second tumors.

Conclusions
We have identified subgroups of non-Hodgkin's lymphoma patients with increased standardized incidence ratios of secondary malignancy and variables that have a negative impact on the time free of second tumors. This information could help physicians to select the most appropriate treatments. Finally, taking into account the possible occurrence of secondary neoplasia, long-term monitoring must be considered.

Key words: second cancer, non-Hodgkin lymphoma, follicular lymphoma, small lymphocytic lymphoma, treatment.

Citation: Sacchi S, Marcheselli L, Bari A, Marcheselli R, Pozzi S, Luminari S, Lombardo M, Buda G, Lazzaro A, Gobbi P, Stelitano C, Morabito F, Quarta G, and Brugiatelli M. Secondary malignancies after treatment for indolent non-Hodgkin's lymphoma: a 16-year follow-up study Haematologica 2008 Mar; 93(3):398-404. doi:10.3324/haematol.12120

Acknowledgments: we are indebted to the Associazione Angela Serra per la Ricerca sul Cancro for financial support. Thanks also to GISL trial office staff and in particular to Orsola Ciarcia and Caterina Mammi, BS, for central data management.

Manuscript received August 13, 2007.
Manuscript accepted November 27, 2007.

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Introduction

Given the now successful treatment of Hodgkin's lymphoma, secondary cancers and late sequelae of this malignancy have been studied extensively.[1] In contrast, relatively little information on secondary cancers is available for non-Hodgkin's lymphomas (NHL) because treatments for NHL have been less effective compared to those for Hodgkin's lymphoma. However, evolving therapies, such as monoclonal antibodies, have improved the prognosis of NHL[2-5] and increased the long-term survival of patients.

Several studies[6-11] (but not all)[12-14] have reported an increased overall risk of secondary cancer after treatments for NHL. The increased risk pertained especially[8,9,11,13] or solely[14] to patients who were relatively young at the time of the first treatment. This elevated risk was due mainly to high incidences of myelodysplastic syndrome/acute myeloid leukemia (MDS/AML)[9,11,13] and solid tumors, including those found in lung, bladder, and the colon.[11,13]

Few of these studies have reported cancer risk beyond 10 years after treatment, and none has focused on indolent lymphoma. Furthermore, the majority of studies are population-based. Although these investigations have analyzed thousands of patients, they utilize cancer registry databases that typically contain little information on clinical baseline characteristics or chemotherapy regimens. In the present study, we analyzed a large cohort of patients with indolent lymphoma who participated in clinical trials at *Gruppo Italiano Studio Linfomi* (GISL) centers. The aim of this long-term follow-up study was to determine the incidence rate and identify risk factors for the development of secondary cancer in a homogeneous group of patients. The clinical characteristics of these patients as well as first-line and subsequent treatments were recorded at the times of diagnosis and recurrence.

Design and Methods

Patients

The GISL maintains a database on the treatment and follow-up of all NHL patients enrolled in clinical trials. Data managers at participating centers routinely update the central GISL database every 3-6 months throughout the trials and every 6-12 months during follow-up. The data managers fill out standardized forms that include information on patients' characteristics, laboratory parameters, treatments, outcome, late toxicity, and the occurrence of second cancers. The data managers describe the observed secondary cancers, which are subsequently codified in Modena. When necessary, additional information can be requested from the investigators. Eligibility criteria for this study were: i) patients with previously untreated NHL with a histologically confirmed diagnosis of follicular lymphoma (FL), small lymphocytic lymphoma (SLL), or marginal zone B-cell lymphoma (MZL), either nodular and extranodular or splenic; (ii) availability of data on clinical characteristics, laboratory parameters, treatments (as reported in Tables 1 and 2), outcome, and the occurrence of second cancers; (iii) availability of follow-up data for more than 6 months after diagnosis.

Between 1988 and 2003, 625 patients with indolent NHL were enrolled in a number of GISL trials. Of these patients, 62 (10%) were excluded: 40 because they did not complete the planned chemotherapy and were immediately lost during the follow-up period, and 22 because of insufficient data (more than 25% of the data missing). Thus, for the purposes of this study, we identified 563 patients with FL, SLL and MZL. The treatment regimens utilized and the number of patients in each trial are summarized in Table 1. Briefly, patients in groups 1-8 were treated with one of the following regimens: chlorambucil +/- prednisone,[15] high-dose chlorambucil + prednisone,[16] high-dose chlorambucil prednisone + epidoxorubicin,[16] fludarabine + cyclophosphamide,[17] methylprednisolone + cyclophosphamide + epidoxorubicin + etoposide + cytarabine + bleomycin + vincristine + methotrexate (ProMECE-CytaBOM),[18] bleomycin + epidoxorubicin + cyclophosphamide + vincristine + prednisone (BACOP),[19] BACOP + fludarabine + mitoxantrone + dexamethasone,[20] or BACOP + fludarabine + rituximab.[21]

All of the GISL trials complied with the requirements of the Declaration of Helsinki and its amendments and were conducted in accordance with Good Clinical Practice guidelines. The protocols were approved by the institutional review board at each participating center. Written informed consent was obtained from all patients. Approval for the present study was obtained from the review board of the GISL. Upon completion of chemotherapy, involved-field radiotherapy was allowed at the treating physician's discretion to irradiate residual masses or the sites of previous bulky or extranodal disease. According to study protocols, the radiotherapy dose was 30-40 Gy.

Statistical methods

Follow-up began at the end of the first treatment for NHL and ended at the date of death, the date of last follow-up evaluation, the date of diagnosis of secondary cancer, or the end of the study (April 30, 2007), whichever occurred first. Secondary cancers were classified by site in accordance with the oncology section of the International Classification of Disease.[22] Individuals who developed malignancies within 6 months of the diagnosis of NHL or had a primary cancer other than NHL were excluded from this analysis.

The primary aims of this research were to determine the incidence of secondary malignancies, the time free of second tumors, and risk factors for the development of

Table 1. Treatment utilized in the 563 patients with indolent lymphoma.

Characteristics	*N. of patients*	*% of patients*	*Person-years at risk*
	563	*100*	*2858*
Chemotherapy regimens			
Chl ± P	72	13	445
HDChl-P	82	14	354
HDChl-PE	82	14	365
FC	38	7	74
ProMECE-CytaBOM	34	6	316
BACOP	88	16	676
BACOP/FND	139	25	368
BACOP/FR	28	5	60
Chemotherapy containing:			
Alkylating (Alk)	154	28	798
Alk + Anthracycline	204	36	1357
Alk + Anthracycline + Fludarabine	205	36	703
Radiotherapy			
No	493	88	2354
Yes	70	12	504
More than one line of treatment			
No	307	54	1488
Yes	256	46	1370

Chl ± P: chlorambucil ± prednisone; HDChl-P: high dose Chl-prednisone; HDChl-PE: HDChl-P plus Epidoxorubicin; FC: fludarabine, cyclophosphamide; ProMECE-CytaBOM: methylprednisolone, cyclophosphamide, epidoxorubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate; BACOP: bleomycin, epidoxorubicin, cyclophosphamide, vincristine, prednisone; BACOP/FND: BACOP plus fludarabine, mitoxantrone, dexamethasone; BACOP/FR: BACOP plus fludarabine, rituximab.

secondary cancer. The incidence of secondary neoplasia per person/year in the study population was compared with the incidence of malignancy in the Italian population, utilizing age-, sex-, and calendar period-specific incidence rates derived from the Italian Institute of Health (*ISS, Istituto Superiore di Sanità*).[23] The standardized incidence ratio (SIR) was calculated from the ratio between the observed and expected numbers of cancers; 95% confidence intervals (95% CI) were based on the assumption that the observed numbers of secondary cancers were distributed as Poisson variables.[24] Absolute excess risk (AER) of secondary cancer was calculated by subtracting the expected from the observed cases and dividing by the number of person-years at risk. AER was expressed per 100 person-years. Cumulative incidences were estimated in the competing-risk model, with death from any cause as the competing event.[25] The time free of second tumors was measured from the end of the first treatment to the last follow-up or to the date of diagnosis of a second tumor and was calculated using a Kaplan-Meier estimate. The Cox proportional-hazards model was used to quantify the effects of different treatments on the risk of secondary cancer within the patient group, adjusting for demographic confounders and stratifying by type of histology (follicular or non-follicular lymphoma), as opposed to the person-years analysis in which risk was compared with that in the general population. The proportional-hazard assumption of risk was checked by graphical analysis of Schoenfeld residuals, and the functional form of co-variates was checked by analysis of Martingale residuals.[26] The level of statistical significance for all tests was set at two-sided $p<0.05$. Over-optimism and calibration of the model was computed over 250 bootstrap replications by means of Harrell's methods.[27] All analyses were performed with the Stata 8.2/SE package.[28]

Results

Patients' characteristics

A total of 563 patients with indolent NHL met the defined eligibility criteria and were included in this analysis. The case record forms had good overall quality; only 14% of the forms lacked data. The 5-year overall survival rates were 82%, 65%, and 85% for patients with FL, SLL, and MZL, respectively, with a median follow-up of 62 months (range, 3-212 months) for all patients and of 70 months for living patients. The number of patients and follow-up times comprised 2858 person-years of risk for a secondary tumor. The median age at diagnosis was 60 years (range, 22-84) and 51% (n=289) of patients were male. All patients were treated with chemotherapy, either alone (88%) or in combination with radiotherapy (12%). The patients' characteristics and treatments are summarized in Tables 1 and 2.

Secondary malignancies

During the follow-up, 39 patients (6.9%) developed a second cancer. A total of 196 patients died, 19 were lost during the follow-up period, and the remaining 348 patients (15 with secondary cancer) survived to the end of the study period. The most common causes of death were progressive disease (56%), secondary cancer (13%), cardiopathy (12%), and infection (5%). No patients developed a third cancer during the follow-up period. Twelve of the 39 patients with secondary cancers developed MDS/AML, and 27 developed solid tumors including lung cancer (n=8), gastro-intestinal cancer (n=7), and other types of cancer (n=12) (Table 3). We did not observe cases of secondary Hodgkin's lymphoma or NHL. However, biopsies with histological examination were not performed in relapsed cases, and further occurrences were usually considered relapses. Thus, the incidence of Hodgkin's lymphoma and of new or transformed NHL could be underestimated. Fourteen of the 39 second malignancies occurred after additional treatments for progressive or recurrent disease. The median time from diagnosis of indolent NHL to diagnosis of a solid tumor was 52 months (range, 16-164 months), and that to diagnosis of MDS/AML was 25 months (range, 6-168 months).

Table 2. Descriptive characteristics of the 563 patients with indolent lymphoma.

Characteristics	*N. of patients*	*% of patients*	*Person-years at risk*
Total	*563*	*100*	*2858*
Age at diagnosis, years			
22-50	133	24	912
51-60	151	27	775
61-70	217	38	966
71-84	62	11	205
Gender			
Female	274	49	1558
Male	289	51	1300
Histology			
Follicular	296	53	1671
Small lymphocytic lymphoma	224	40	1092
Marginal zone*	43	7	95
Period of first treatment			
1988-1994	187	33	1407
1995-1999	181	32	904
2000-2003	195	35	547
FLIPI score#			
0-2	341	66	1977
3-5	178	34	646
Bulky disease			
No	513	91	2688
Yes	50	9	170
B-Symptoms			
No	476	85	2478
Yes	87	15	380
Extranodal sites of disease			
0-1	399	71	2204
> 1	164	29	654
Follow-up			
5 years or less	279	581	
more than 5 years	284		2277
more than 10 years	78		929

**Splenic or nodal and extanodal marginal zone B-cell lymphoma; #missing data for 44 of 563 cases (7.8%).*

Table 3. Cases and sites of secondary cancer.

Second tumor	*ICD-9 code*	*N. of patients*	*% of patients*	*Person-years at risk*
MDS/AML	238.72-238 73-205-208	12	2.1	40
Lung	162	8	1.4	51
Digestive tract	151-153-154-155-157	7	1.2	36
Breast	174	2	0.4	14
Larynx	161	2	0.4	2
Prostate	185	2	0.4	11
Bladder	188	2	0.4	12
Ovaries	183	1	0.2	2
Adrenocortical glands	194	1	0.2	3
Melanoma	172	2	0.4	5
Total n. of tumors		39	6.9	2858
No second tumors		524	93.1	2682

ICD-9: International Classification of Diseases 9th Edition. http://www.cdc.gov/nchs/icd9.htm

Table 4. Standardized incidence risk and absolute excess risk of second cancer analyzed according to demographics and treatment (34 cases out of 39)*.

Factor	*Observed*	*Expected*	*SIR (95%CI)*	*AER*	*p°*
Gender					
Female	9	8.2	1.10 (0.50-2.10)	+0.05	0.016
Male	25	9.2	2.72 (1.76-4.02)	+1.01	
Age at first treatment					
<65	23	8.6	2.66 (1.69-4.00)	+0.68	0.037
65+	11	8.7	1.26 (0.63-2.26)	+0.32	
Histology					
FL	20	7.76	2.58 (1.58-3.98)	+0.73	0.251
SLL	13	8.70	1.49 (0.80-2.55)	+0.39	
MZL	1	0.87	1.15 (0.03-6.43)	+0.14	
Chemotherapy-containing					
Alkylating (Alk)	10	6.50	1.54 (0.74-2.83)	+0.44	0.074
Alk+anthracycline	11	7.02	1.57 (0.78-2.80)	+0.29	
Alk+anthracycline+ fludarabine	13	3.81	3.41 (1.81-5.83)	+1.31	
Radiotherapy					
No	28	14.9	1.88 (1.25-2.71)	+0.54	>0.50
Yes	6	2.40	2.48 (0.91-5.40)	+0.72	
Period of first treatment					
1988-1994	15	8.66	1.73 (0.97-2.86)	+0.45	>0.50
1995-1999	10	5.40	1.85 (0.89-3.40)	+0.51	
2000-2003	9	3.26	2.76 (1.26-5.23)	+1.05	

*SIR: standardized incidence risk. AER: absolute excess risk. *Five MDS cases were excluded. °Chi-squared test for unequal SIR.*[29]

Incidence of secondary malignancy

The overall risk of secondary malignancy in patients with indolent NHL was higher than the risk of malignancy in the general Italian population (SIR 1.9; 95% CI: 1.4-2.7). As shown in Table 4, the overall incidence of malignancy was highest in male patients (SIR 2.72; 95% CI: 1.76-4.02, p=0.016), and in patients who were under 65 years old at the time of their first treatment (SIR 2.66; 95% CI: 1.69-4.0, p=0.037). In the subgroup with follicular histology (SIR 2.58; 95% CI: 1.58-3.98), and in patients treated with radiotherapy (SIR 2.48; 95% CI: 0.91-5.40), the SIR were increased, but not to a statistically significant extent (p>0.05).

The overall risk of secondary malignancy was increased for each treatment modality, but achieved marginal significance (p=0.074) for treatments containing fludarabine. Interestingly, the increase in risk of secondary malignancy observed in patients treated in 2000-2003 coincided with the introduction of fludarabine in GISL chemotherapy regimens (Table 4).

The risk of secondary malignancy relative to age at diagnosis of the second cancer is shown in Table 5. An increased risk of secondary cancer was detected in the cohort groups aged 45-54 (SIR 4.91; 95% CI: 2.2-10.1, AER 0.78) and those aged 55-64 (SIR 3.41; 95% CI: 1.98-5.87, AER 1.05). The cumulative incidences of secondary malignancy, including MDS/AML, were 6.6%, 9.5%, and 15.3% at 5, 8, and 12 years, respectively,

estimated using the Kaplan-Meier method. After correction in a competing-risk model by Gooley's method, the cumulative incidences of secondary malignancy were reduced to 5.5%, 6.5%, and 10.5% at 5, 8, and 12 years, respectively (Figure 1).

Risk factors for developing a secondary malignancy

The probabilities of remaining free of a second tumor estimated at 5, 8 and 12 years were 93%, 90% and 85%, respectively. In a univariate Cox regression model, the factors that had a significant negative impact ($p<0.05$) on time free of a second tumor were older age at first treatment (a hazard ratio (HR) increment of 1.9 was associated with each 10-year increment above the median age), male sex, and fludarabine-containing therapy. Factors that did not significantly influence time free of a second tumor included the Follicular Lymphoma International Prognostic Index (FLIPI) score, which takes into account elevated lactate dehydrogenase levels, the presence of more than four nodal sites of disease, clinical stage III-IV disease, age >60 years, and other baseline characteristics of the patient such as bulky disease, more than one extranodal site, and B-symptoms. Thus, we did not consider these factors as potential confounders.

In order to evaluate the impacts of variables with significant influences further, we performed a Cox regression analysis stratified by histology, utilizing age at first treatment in a continuous form scaled by the median age of the population (60 years). This multivariate analysis confirmed the prognostic values of age, male gender, and fludarabine-based treatment, as demonstrated by statistically significant hazard ratios (Table 6). The model showed good performance, with a shrinkage factor of 0.994 and an unbiased discriminating power (C-statistic of 0.723; 95% CI: 0.863-0.604) over 250 bootstrap replications. Furthermore, the regression coefficient showed an acceptable shrinkage factor (>0.9), considering the small number of observed events.

In a separate analysis, the univariate Cox regression analysis of time free of second tumor indicated that MDS/AML was detected mainly in male patients (HR: 6.2, $p=0.02$) and in patients older than 60 years (HR: 5.7, $p=0.026$). Treatments that included fludarabine did not appear to be associated with the development of MDS/AML. The development of solid tumors did, however, appear to be associated with male gender (HR: 4.04, $p=0.002$) and to fludarabine containing treatments (HR: 3.1, $p=0.013$). Lung cancer was principally associated with male gender (HR: 12.5, $p=0.021$).

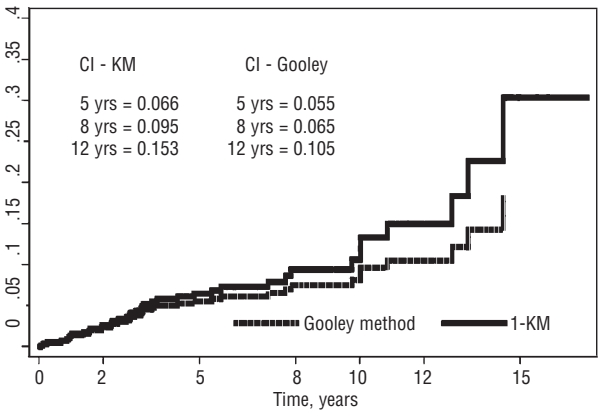

Figure 1. Cumulative incidence of second cancer by the Kaplan-Meier (CI - KM) estimation compared to cumulative incidence according to Gooley (CI - Gooley).

Table 5. Standardized incidence risk (SIR) and absolute excess risk (AER) of second cancer (34 cases out of 39) related to age-, and calendar period- specific incidence. Data derived from the ISS* database, by ICD-9 coding from 140 to 208.

Cohort age	*Person-yrs*	*Observed failures*	*Expected failures*	*SIR*	*95% C.I.*	*AER*
20-44	363	0	0.04	-	-	-
45-54	615	6	1.22	4.91	2.20-10.9	+0.78
55-64	878	13	3.81	3.41	1.98-5.87	+1.05
65-74	885	12	9.64	1.24	0.71-2.19	+0.27
75+	170	3	2.8	1.06	0.34-3.28	+0.09
Total	2911	34	17.6	1.94	1.38-2.71	+0.56

**ISS: Istituto Superiore di Sanità (Italian Institute of Health).*

Table 6. Cox regression model stratified by type of histology with bootstrap validation.

Covariate	*Coefficient*	*SE*	*HR*	*p*	*Bootstrap validation (B=250)* *Unbiased Coeff.*	*Shrinkage*
Age*	0.073	0.019	2.08*	<0.001	0.067	0.93
Gender M**	1.530	0.394	4.62	<0.001	1.392	0.91
Fludarabine use**	0.957	0.429	2.60	0.026	0.895	0.94
C-statistics	0.757 (95%CI 0.685-0.828)				0.723 (95%CI 0.604-0.843)	
Shrinkage factor (model)	0.944					

**Age in continuous form scaled at the median (60 years old), HR referred to increasing age by 10 years; **gender code: F=0, M=1; fludarabine use code: not used=0, used=1.*

Discussion

In the present study, we analyzed a large and homogeneous cohort of patients with indolent lymphoma who participated in clinical trials at GISL centers. These trials spanned more than 15 years. Data on patients' demographics, baseline characteristics, histology, clinical stage, and treatments were recorded prospectively in the GISL database at the times of diagnosis, recurrence, and follow-up evaluation. However, results must be interpreted cautiously because they could be biased by the retrospective nature of the study. As data managers at participating centers were not urged to specifi-

cally report on secondary cancer, our results could slightly underestimate the risk of secondary cancer. Overall, the risk of secondary malignancy, excluding MDS, was only slightly higher than the risk of malignancy observed in the general population. However, including MDS/AML, 39 secondary tumors were observed and the 12-year cumulative incidence rate, after correction in a competing-risk model, was 10.5%.

MDS/AML and lung cancer, mainly occurring in men, accounted for more than 50% of the total number of secondary malignancies. The risk of a second tumor was increased significantly in the male population. Our results also show an increased risk of malignancy in patients 45-64 years old; the risk in patients older than 65 matched that in the general population. The overall relative risk of secondary malignancy was increased for each treatment modality but was particularly elevated, although with marginal statistical significance, in patients treated with fludarabine-based chemotherapy. Surprisingly, treatments that included fludarabine did not appear to be associated with the development of MDS/AML.

Factors that had a significant negative impact on time free from a second tumor included age at first treatment, male sex, and fludarabine-containing therapy. A Cox multivariate regression analysis stratified by histology and utilizing age in a continuous form scaled by the median confirmed the prognostic risk factors of age at the time of diagnosis, male gender, and fludarabine-based treatment.

In conclusion, based on a retrospective analysis, we have identified subgroups of patients with increased SIR and variables that have a negative impact on time free from a second tumor. If considered together with traditional prognostic factors and possible side effects of treatment, this information can help physicians to determine the most appropriate treatments. Finally, taking in to account the possible occurrence of secondary neoplasia, long-term monitoring should be considered.

Authorship and Disclosures

SS, conception and design of the study, acquisition, analysis and interpretation of the data, final approval of the version to be published. LM and RM: statistical analysis, data collection, interpretation of data and creation of tables and figures. SS and LM wrote the manuscript. SS, AB, SP, SL, ML, GB; AL, PG; CS, FM, GQ, and MB participated in the patients' care, data recording, and the interpretation and analysis of data. All authors contributed critically to the drafting of the article, and approved the final version. The authors reported no potential conflicts of interest.

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