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The risk of acute leukemia in patients treated for Hodgkin's disease is significantly higher after combined modality programs than after chemotherapy alone and is correlated with the extent of radiotherapy and type and duration of chemotherapy: a case-control study

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Abstract

Background and Objective. **Patients treated for Hodgkin's disease have an increased risk of developing subsequent acute leukemia. This coopoerative study was conducted to assess the relative risk associated with several candidate factors including age, splenectomy, combined modality therapy and cumulative drug dose including alkylating agents and nitrosurea derivatives.**

Design and Methods. **This study evaluated the risk of acute leukemia according to pretreatment variables and therapy modalities among 1659 patients treated for Hodgkin's disease and followed for a median time of 10 years. Both case-control and actuarial risk studies were performed. Median age was 34 years (range: 12-83); 53% of patients were splenectomized. As to the overall therapy, 348 patients (21%) were given radiotherapy (RT) alone, 375 (23%) chemotherapy (CT) alone (including MOPP, MOPP+ABVD or MOPP+ ABVD+ lomustine); 936 (56%) received both CT and RT, either as primary or salvage treatment.**

Results. **The overall 15-year actuarial risk of leukemia was 4.2%; the hazard function curve showed two peaks of risk at the 3th and the 8th year from the initiation of therapy and no leukemia beyond the 12th year of follow-up. Risk of leukemia was 0.3% after RT alone, 2.8% after CT alone (2.2% after MOPP; 4.4% after MOPP+ ABVD+ lomustine), and 5.4% in patients given combined modality therapy (10.2% for RT+ MOPP; 15.6% for RT+ MOPP+ lomustine). No leukemia occurred after ABVD alone and the risk was low (0.6%) when neither mechlorethamine nor lomustine were utilized. Patients who had received extended radiotherapy including abdomen and pelvis in addition to MOPP showed a significantly higher risk of leukemia compared to those given limited RT+MOPP (P = 0.01). Case-control analysis indicated advanced stage, type and duration (> 8 months) of CT and extension of RT as significant risk factors for leukemia. Compared to RT alone, the odds ratio was 5.9 after MOPP+extended RT, and 8 when a lomustine-containing regimen was used, as well. Neither age nor splenectomy were independent risk factors for leukemia; splenectomy was influential only when patients had been given MOPP chemotherapy, as well.**

Interpretations and Conclusions. **Both case-control and actuarial analyses indicated that: a) combined modality therapy with MOPP and extensive RT (including abdomen and pelvis), and the use of lomustine added to the leukemogenic risk of MOPP alone; b) programs without mechlorethamine, procarbazine and lomustine were almost devoid of leukemogenic risk.**

Key words: Hodgkin's disease, risk of leukemia, secondary leukemia

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Patients treated for Hodgkin's disease have an increased risk of developing subsequent myelodysplasia and acute leukemia.[1-20] Although this risk is multifactorial, a direct leukemogenic effect of therapy can play an important role in the pathogenesis of this severe long-term complication.[21-26] In the last twenty years, numerous studies have reported on the issue of secondary leukemia and myelodysplasia in Hodgkin's disease and some facts are well known and uncontroversial. Actuarial analysis has indicated an overall 10-year risk of leukemia ranging between 2% and 11% of total, with significant differences according to the type of therapy received. The risk of leukemia in patients who have been treated with megavoltage radiotherapy (RT) alone is minimal, if anything, while chemotherapy (CT) with alkylating agents and procarbazine bears the most significant risk.[7-18,27-29] Of interest, no increased risk of leukemia has been observed after a CT regimen, such as the ABVD one, which does not contain alkylating agents or procarbazine.[11,13,18] Moreover, there is a *critical window* for the development of leukemia and

patients surviving for more than 11 years after treatment appear to be at no increased risk of this late complication.[30]

There remain, however, some controversial points to be answered conclusively. One of these concerns the influence of age at diagnosis on the risk of subsequent leukemia; several studies found a higher risk of leukemia in patients treated beyond the age of 40,[5-7,13,31] while others failed to confirm this finding.[16-18] In some reports, splenectomy and splenic irradiation correlated with an increased risk of developing myelodysplasia and leukemia;[17,31-33] this observation, however, needs to be confirmed on a large group of patients homogeneously treated and followed-up.

Moreover, no clear-cut conclusions have yet been reached on several points including: a) whether combined modality therapy adds to the risk of CT alone with alkylating agents, as indicated by some studies;[13-16] b) whether a relationship can be demonstrated between the cumulative dose of drugs or the extent of RT and the magnitude of leukemia risk;[29,34-36] c) whether other drug categories such as nitrosourea and/or podophyllotoxin derivatives may significantly increase the risk associated with alkylating agents, as previously described.[16,36]

To answer some of these open questions, we pooled the data of two series of patients affected by Hodgkin's disease, diagnosed and treated from 1975 to 1992 at the Institutes of Hematology of the Universities of Pavia and Rome, and followed-up for a median time of 10 years. In our Institutions, staging and treatment policies were fairly uniform and have changed over time in a similar way; all patients were seen at our out-patient clinics on a regular basis. The study design included a matched case-control analysis, as well as the analysis of actuarial risk of leukemia for the assessment of risk factors.

Materials and Methods

Patients

Between 1975 and 1992, 1661 consecutive patients affected with Hodgkin's disease were admitted to the Institute of Hematology of the University of Pavia (607 patients) or to the Hematology Istitute and Radiation Oncology of the University "La Sapienza" of Rome (1054 patients). For the purpose of this study, we pooled all clinical and therapeutic information in a single data base and analyzed the results irrespective of the Institution of origin.

Histologic diagnosis and classification were made according to the Rye criteria. All patients underwent clinical staging with history, physical examination, chest X-ray, complete blood count and blood biochemistry. Bipedal lymphoangiography was done before 1984; afterwards, all patients underwent computerized tomography of chest, abdomen and pelvis. All patients underwent bone marrow biopsy and 53% of total were surgically staged with splenectomy, liver biopsy and evaluation of para-aortic, pelvic and iliac lymph nodes. Table 1 illustrates the main characteristics of the study population at the diagnosis of Hodgkin's disease. The male to female ratio was 1.2 and median age was 34 years (range: 12-83 years); 46% of patients presented with advanced disease and 43% had systemic symptoms. Nodular sclerosis and mixed cellularity were the predominant histologies (46% and 34%, respectively). Splenectomy was performed in 53% of cases as a surgical staging procedure, while the spleen was irradiated in 6% of cases.

Table 1. Characteristics of the study population.

Characteristics	*No. of patients*	*%*
Total	1661	
Male-female ratio	1.2	
Median age (years)	34 (12-83)	
Systemic symptoms	712	43
Stage		
I-II	903	54
III-IV	758	46
Histology		
Lymphocyte predominance	141	9
Nodular sclerosis	763	46
Mixed cellularity	570	34
Lymphocyte depletion	119	7
Unclassified	68	4
Splenectomy	880	53
No splenectomy	679	41
Splenic irradiation	102	6

Therapy groups

The patients evaluable for therapy in this study were 1659; two cases died of laparotomy-related complications before a therapy could be initiated. Treatment information included the following: date of first treatment, type of first treatment, date of recurrence (if any), type of salvage therapy, overall duration of therapy in months (primary + salvage therapy in relapsed patients), date of the last follow-up or death, disease status at the last follow-up, cause of death, date of diagnosis of acute leukemia. Information on type and dose of the chemotherapeutic agents and data on irradiated areas and dosimetry were available for all patients. To evaluate the association between the risk of leukemia and the type of treatment, patients were subdivided according to the overall treatment they had received to date. Accordingly, four main treatment categories were defined as follows: RT alone which comprised patients who had never received chemotherapy; CT alone which comprised patients who had never received RT; adjuvant combined modality therapy which referred to patients who had received both RT and CT as front-line therapy, with no recurrences of disease, and salvage combined modal-

ity therapy which referred to patients who had been given both RT and CT at different times for recurrences of their disease. Each patient was assigned to a single treatment category and patient-years ($\sum$ of months of follow-up/12) for each category were calculated. Radiotherapy alone was delivered to 348 patients (21% of total) and CT alone to 375 patients (23%); 936 patients (56% of total) received both modalities during the entire course of their disease, either as adjuvant combined therapy (510 patients, 31%) or as salvage therapy (426 patients, 25%). A detailed categorization of the overall therapy groups is illustrated in Table 2. There were no major differences in the treatment policies between the two Institutions and the majority of patients were treated according to the on-going clinical trials. Radiotherapy was administered by a Cobalt-60 source or by a linear accelerator with a standard technique and dosimetry: 40-44 Gy/field to involved fields; 30-36 Gy/field to non-involved nodal sites. Radiotherapy alone was utilized in patients with early pathological stage (I-II); the large majority (73%) of patients given RT alone received extended-field irradiation including mantle, para-aortic and iliac nodes with (total nodal irradiation) or without inguinal nodes (subtotal nodal irradiation). Up to 1983, both in Pavia and Rome, the combination of mechlorethamine, vincristine, procarbazine and prednisone known as MOPP[37] was by far the most commonly used CT regimen. Afterwards, the ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) combination[38] was introduced, either alone or alternating with MOPP.[39] Subsequent modifications consisted of substitution of cyclophosphamide for mechlorethamine (COPP) or dropping of mechlorethamine (OPP) from the original MOPP combination or dropping of dacarbazine (ABV) from the original ABVD combination. In the CT alone category, the MOPP group accounted for 33% of patients, while 44% of patients received both MOPP and ABVD, either as part of a front-line alternating CT program, or at different times during the course of their disease (more often ABVD as salvage after MOPP). Only a small proportion of patients (7%) received ABVD alone, while a significant proportion of patients (16%), in addition to MOPP and ABVD (either alternating or in sequence), were given a combination of lomustine, etoposide and melphalan (CAV regimen) as conventional salvage therapy for multiple relapses.[40] As far as combined modality therapy is concerned, 40% of patients of this group received mantle or mantle + para-aortic nodes irradiation, 26% and 15% received TNI or STNI. Irradiation was limited to the inverted Y area in 4% and to involved fields in 15% of patients, respectively. Among patients given combined modality therapy, 30% received MOPP, 28% MOPP and ABVD, 8% OPP and ABVD, either alternating or in sequence, and 14% ABVD alone in addition to RT. A small group of patients (8%) was represented by those who had multiple relapses and received lomustine, etoposide and melphalan as conventional salvage chemotherapy after RT, MOPP and ABVD. No patient in our study cohort received lomustine as part of a conditioning regimen for stem cell transplantation.

Table 2. Overall therapy groups and actuarial risk of leukemia.

Therapy groups	*No. of patients*	*%*	*No. of leukemias*	*15-yr actuarial risk of leukemia %*
RT alone	348		2	0.3
Mantle ± PA	85	24	0	0
Inverted Y	10	3	0	0
STNI or TNI	253	73	2	0.6
CT alone	375		7	2.8
MOPP	124	33	3	2.2
ABVD	24	7	0	0
MOPP+ABVD	166	44	1	0.8
MOPP+ABVD+CAV	61	16	3	4.4
Combined modality therapy	936		27	5.4
RT field size				
Involved field	140	15	1	0.9
Mantle±PA	374	40	5	3.8
Inverted Y	39	4	1	5.2
STNI or TNI	383	41	20	8.9
Type of CT				
MOPP	277	30	18	10.2
ABVD	129	14	1	0.3
MOPP+ABVD	263	28	0	0
OPP+ABVD	71	8	1	0.4
COPP+ABV+IMEP	74	8	1	0.6
MOPP+ABVD+CAV	79	8	6	15.6
Others	43	4	0	0
Total	1659		36	4.2

ABVD = adriamycin, bleomycin, vinblastine, dacarbazine; CAV= lomustine, melphalan, etoposide; COPP = cyclophosphamide, vincristine, procarbazine, prednisone; IMEP = ifosfamide, methotrexate, etoposide, prednisone; MOPP = mechlorethamine, vincristine, procarbazine, prednisone; OPP= vincristine, procarbazine, prednisone; STNI = subtotal nodal irradiation; TNI = total nodal irradiation.

Statistical analysis

We calculated the period of risk for development of acute leukemia as the time between the initiation of first therapy for Hodgkin's disease (either RT or CT) and the date of the last follow-up or the date of diagnosis of acute leukemia. Patients developing acute leukemia were considered as failures; the other patients were considered as censored observations at the time of the last-follow-up. Analysis of the actuarial risk of leukemia was performed,[41] as well as the hazard of leukemia function at yearly intervals; the

hazard was expressed as events per person-months. Different risk groups were compared with the log-rank test.

Due to the low number of events, a case-control study was preferred for the assessment of the relative risk associated with the several candidate factors.[42] Case patients were defined as those whose leukemia was diagnosed at least six months after the end of primary therapy for Hodgkin's disease. For each case patient, four matched controls treated for Hodgkin's disease who did not develop acute leukemia were selected. The matching variables included age (±5 years), years of diagnosis (before or after 1980) and duration of the follow-up (±5 years). Because all patients received some form of therapy (radiotherapy, chemotherapy or both), we did not have a reference group of subjects who had never been exposed to leukemogenic agents. Therefore, the comparison of the effect of chemotherapy and of combined modality treatment on the risk of leukemia was relative to patients treated with radiotherapy alone. Conditional logistic regression analysis was used to estimate odds ratio (OR) and their 95% confidence intervals for the candidate risk factors; EGRET (SERC and CYTEL, Seattle, USA) statistical software was used for computation.

Diagnosis of myelodysplasia and of acute leukemia

Hematologic survey on peripheral blood was done every three months; marrow aspirates were performed whenever deemed necessary for unexplained cytopenia or any other hematologic abnormality in peripheral blood. Myelodysplasia and/or acute leukemia were diagnosed and morphologically classified according to the FAB criteria.[43,44] Bone marrow biopsies were analyzed with special reference to the cellularity and the presence of micromegakaryocytes, fibrosis and lymphoid infiltration; cytogenetics were performed on 30 cases.

Results

Actuarial risk of leukemia

Actuarial analysis included 1659 patients treated for Hodgkin's disease, with a median follow-up of 10 years (range: 24-274 months). At the time of this analysis, 1255 patients (76%) were in complete remission, while 404 had residual or recurrent Hodgkin's disease. During the entire follow-up time, 36 patients (2.2% of total) developed a subsequent acute leukemia; in all but one case, acute leukemia was preceded by a myelodysplastic phase (preleukemia). The median time from the initiation of therapy for Hodgkin's disease to subsequent myelodysplasia was 54 months and the median time to overt acute leukemia was 60 months (range: 15-144 months). For the entire cohort of patients, the 15-year actuarial risk of subsequent leukemia was 4.2%. Figure 1A illustrates the curve of the overall leukemia risk and Figure 1B illustrates the curves of leukemia risk according to the main therapy categories: radiotherapy alone, chemotherapy alone and combined modality therapy. The actuarial 15-year risk of leukemia in the different overall therapy groups is indicated in Table 2. Among patients treated with RT alone, the actuarial risk was 0.3% (2 cases out of 2490 patient-years). Among patients treated with CT alone, the 15-year risk of leukemia was 2.8% (7 cases out of 2320 patient-years); all cases developing subsequent leukemia had been treated with a CT including the MOPP combination, either alone (actuarial risk of 2.2%) or followed by ABVD and CAV regimens for recurrences of disease (actuarial risk of 4.4%). No cases of acute leukemia occurred among patients treated with the ABVD regimen alone.

The overall 15-year risk of leukemia in patients given combined modality therapy was 5.4%. No difference in the actuarial risk of developing leukemia was found according to whether combined modality therapy was administered in an adjuvant or salvage setting. Patients who had received RT+MOPP showed a 10.2% actuarial risk of leukemia. The highest risk of subsequent leukemia (15.6%) was observed among patients who had received MOPP and RT as primary therapy followed by salvage regimens including ABVD and CAV for multiple recurrences of disease. Only one case of leukemia occurred among patients who had received RT and the ABVD regimen; likewise, the actuarial risk of subsequent leukemia was low (less than 1%) after CT regimens without mechlorethamine such as OPP or COPP. The analysis of the relation between leukemia risk and RT field size indicated that the large majority of patients developing leukemia had been given total nodal or subtotal nodal irradiation or radiation to the abdomen and pelvis. Altogether, patients who had been given TNI/STNI in addition to CT showed a 8.9% actuarial risk of leukemia (12.5% in patients given TNI/STNI and MOPP chemotherapy; data not shown).

Table 3 illustrates the results of the log-rank test for leukemia risk factors. Age was of borderline significance ($p = 0.04$) when a cut-off at 30 years was used; at variance, age was not significant for a cut-off at 40 years. Stage, histology and splenectomy were not significant variables, whereas the type of therapy was influential on the risk of secondary leukemia. A significantly higher risk was demonstrated among patients treated with CT versus those treated with RT alone ($p = 0.04$) and among those treated with a combined modality therapy versus those treated with CT alone ($p = 0.05$). Combined modality therapy including MOPP and RT (MOPP followed by adjuvant RT or RT followed by adjuvant MOPP, or MOPP as salvage after RT) was significantly more risky than therapy including RT and MOPP/ABVD or RT and ABVD ($p = 0.002$; Figure 2). Patients who had received lomustine as part of a conventional salvage

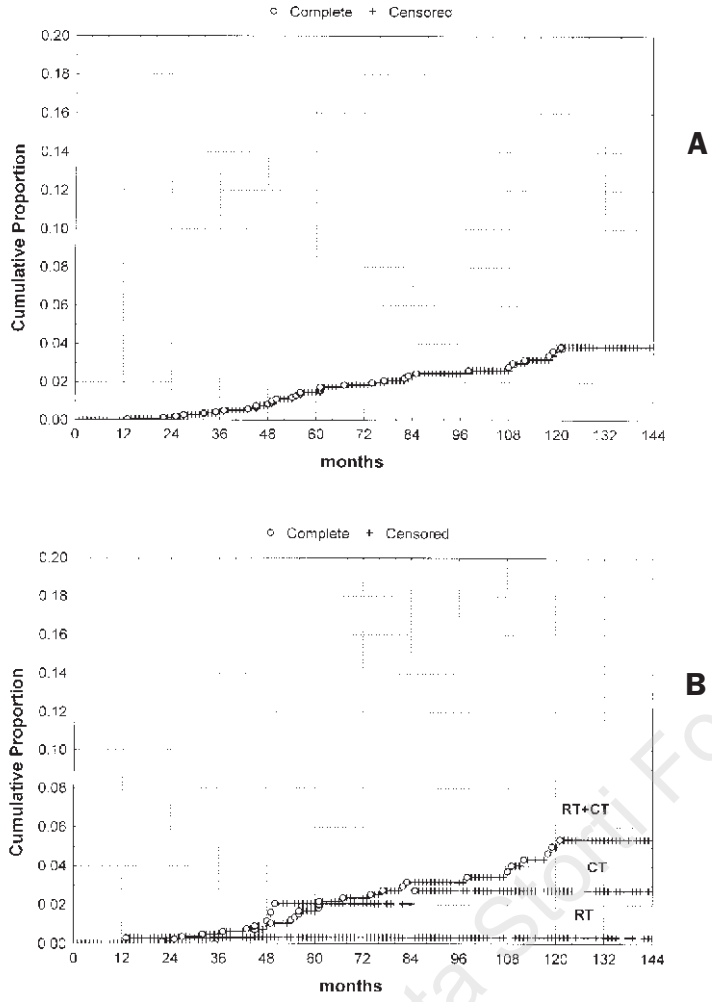

Figure 1. A: Actuarial risk of leukemia for the entire cohort. B: Actuarial risk of leukemia according to main therapy categories.

Table 3. Results of the log-rank test.

Variables	*p value*
Age ≤ 30 vs > 30 yrs	0.04
Age ≤ 40 vs > 40 yrs	ns
Splenectomy vs no splenectomy	ns
RT alone vs CT alone	0.04
CT alone vs combined modality therapy	0.05
Limited RT+MOPP vs extended RT+MOPP	0.01
RT+MOPP vs RT+ABVD or RT+MOPP/ABVD	0.002
Salvage therapy including lomustine vs no lomustine	0.05
Overall duration of CT < 6 vs ≥ 6 mos	ns
Overall duration of CT < 8 vs ≥ 8 mos	0.02

therapy (CAV regimen) after receiving MOPP or MOPP/ABVD had a significantly higher risk of subsequent leukemia than those who had not been given lomustine (p = 0.05).

The extent of radiotherapy and the overall duration of chemotherapy were also demonstrated to be significant risk factors for subsequent leukemia in patients receiving combined modality therapy. Patients who had been given total or subtotal or nodal irradiation including the abdomen and pelvis in addition to MOPP had a significantly higher risk of leukemia than patients who had been given limited radiotherapy in addition to MOPP (P = 0.01). Moreover, the additive effect of RT on the risk of leukemia compared to CT alone was evident only for patients receiving extended radiotherapy including irradiation of the abdomen and pelvis. As far as the influence of CT duration is concerned, a significant cut-off was found at 8 months; patients who had received CT, either as primary therapy or primary plus salvage, for more than 8 months were at higher risk (7% at 15 years) of subsequent leukemia compared with those

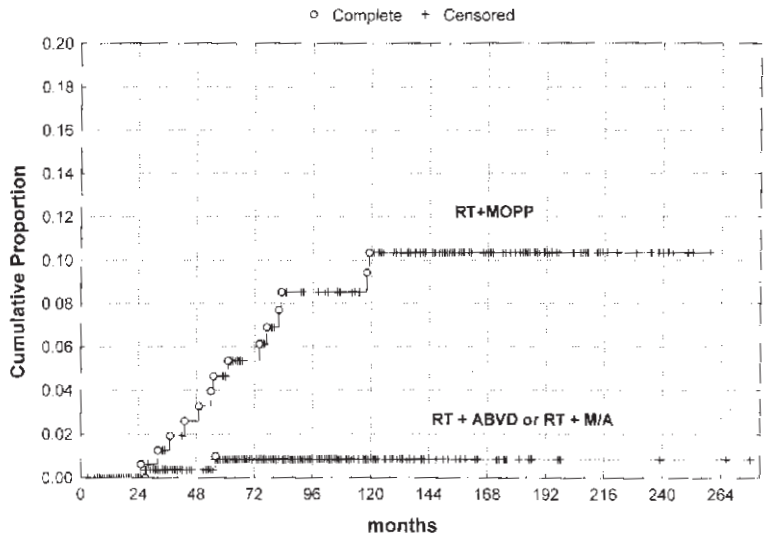

Figure 2. Actuarial risk of leukemia in the combined modality therapy group according to the type of chemotherapy.

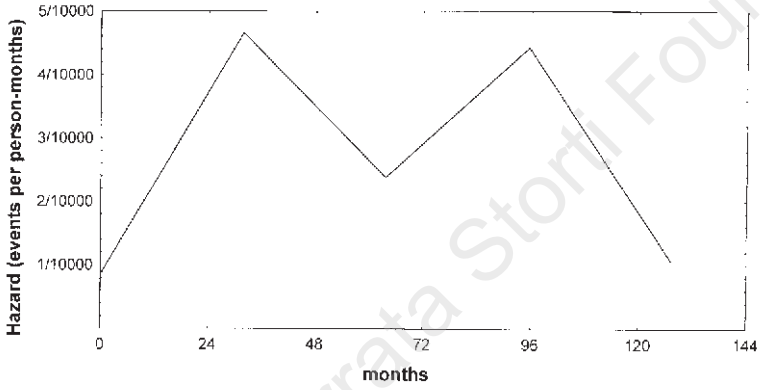

Figure 3. Leukemia hazard function curve for the entire cohort.

who had been given CT for a shorter time (2.8% at 15 years; p = 0.02).

Hazard function

Figure 3 illustrates the hazard function curve for subsequent leukemia in the whole series of patients; this curve showed two peaks of risk at the 3rd and the 8th year from the initiation of therapy, with a sharp decline of risk thereafter, and no cases of leukemia after the 12th year of observation; only one case of leukemia developed after the 10th year from the end of therapy.

Case-control study

Table 4 indicates the distribution of leukemia cases and of controls according to the main patient characteristics and overall therapy groups. Only 6% of the cases were treated with RT alone as compared to 24% of the controls; more than half (53%) of the cases had been given RT and MOPP as compared with 19% of controls. Table 5 illustrates the results of the univariate conditional regression analysis. Neither age with a cut-off at 40 years, nor splenectomy were independent variables for risk of leukemia. At variance, the case-control analysis indicated a significant influence of advanced-stage versus early-stage disease (OR = 2.3; p = 0.03), of combined modality therapy (OR = 6.4; p = 0.02) and CT alone (OR = 4.1; p = 0.05) versus RT alone taken as the reference group. In the combined modality therapy group, the MOPP combination + extended RT, either as adjuvant or salvage therapy, conferred a risk of leukemia 5.9 times higher than that given by chemotherapy without alkylating agents and procarbazine (p = 0.001). Among patients who received combined RT and CT as conventional salvage therapy, the use of a lomustine-containing regimen (CAV chemotherapy) significantly added to the risk of MOPP and MOPP/ABVD (OR = 8; p = 0.05). Moreover, the overall duration of CT (primary or primary + salvage therapy) demonstrated a cumulative effect on

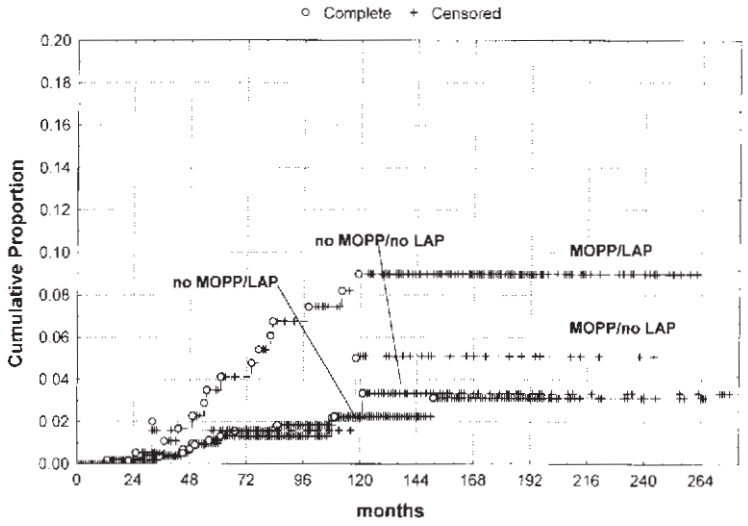

Figure 4. Actuarial risk of leukemia according to splenectomy (LAP) and MOPP chemotherapy status.

the risk of subsequent leukemia; a significant cut-off was found for an overall CT duration of 8 months (OR =1.4; p = 0.04).

The potential role of splenectomy on the risk of secondary leukemia was evaluated among patients who had received a combined modality therapy including the MOPP regimen. For the purpose of conditional regression analysis, we assumed as reference group the patients who had not been splenectomized nor had been given MOPP (no MOPP, no splenectomy). The odds ratios of the groups of patients obtained combining the splenectomy and MOPP status are reported in Table 5. Splenectomy was influential on the risk of leukemia only in patients who had received MOPP chemotherapy (OR = 7.2; p = 0.002). Figure 4 illustrates the actuarial risk of leukemia of the four groups of patients resulting from the combination of laparotomy and MOPP status (no laparotomy, no MOPP; no laparotomy with MOPP; laparotomy, no MOPP; laparotomy and MOPP); the two groups of patients who had been

Table 4. Distribution of the cases and the controls.

Characteristics	*No.of cases*	*%*	*No. of controls*	*%*
Total	36		144	
Men	20	56	75	52
Women	16	44	69	48
Age at diagnosis (years)				
≤ 40	26	72	107	74
> 40	10	28	37	26
No symptoms	20	56	77	53
Systemic symptoms	16	44	67	47
Histology				
Lymphocyte predominance	2	6	14	10
Nodular sclerosis	12	33	67	46
Mixed cellularity	13	36	46	32
Lymphocyte depletion	7	19	8	6
Unclassified	2	6	9	6
Stage				
I-II	15	42	89	62
III-IV	21	58	55	38
Splenectomy	25	69	86	60
No splenectomy	10	28	49	34
Splenic irradiation	1	3	9	6
Overall therapy groups				
RT alone	2	6	35	24
MOPP±RT	19	53	27	19
ABVD±RT	0	0	1	7
MOPP+ABVD±RT	5	14	52	36
MOPP+ABVD+Iomustine±RT	6	17	10	7
Others	4	11	19	13

Table 5. Conditional logistic regression analysis.

Variables	*OR*	*95% CI interval*	*p value*
Age > 40 years	1.07	0.7-1.5	ns
Stage III-IV	2.3	1.1-5	0.03
Splenectomy	1.4	0.6-3.3	ns
Therapy category			
CT alone	4.1	1.1-2.2	0.05
Combined modality	6.4	1.4-29	0.02
Combined modality			
MOPP+extended RT	5.9	2.3-12	0.001
MOPP+Iomustine	8	4-25	0.05
Overall CT duration ≥ 8 mos	1.4	1.1-2.2	0.04
No MOPP-Splenectomy	0.9	0.3-2.6	ns
MOPP-No Splenectomy	3.4	0.5-22	ns
MOPP and Splenectomy	7.2	2.1-25	0.002

OR: odds ratio; CI: confidence interval.

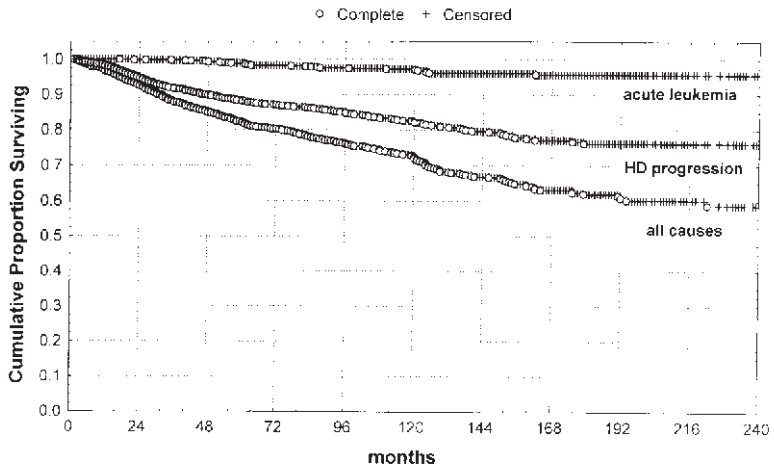

Figure 5. Overall survival for the entire cohort. Contribution to mortality of the specific causes of death.

given MOPP had a significantly higher risk of leukemia than patients who had not, irrespective of splenectomy status.

Causes of death

Figure 5 indicates the actuarial survival of the entire cohort of patients and the contribution of specific causes of death to the actuarial mortality. The 20-year actuarial survival was 59% considering all causes of death (all causes curve) and 77% considering only deaths due to progression of disease (HD progression curve). Acute leukemia accounted for less than 5% of the actuarial mortality. The incidence of the different causes of death is illustrated in Figure 6. At the time of this analysis, there had been 411 fatal events (25% of total patients). Progression of Hodgkin's disease was the cause of death in 243 patients and accounted for 59% of total fatal events; acute leukemia and solid tumors accounted for 8% and 6% of total deaths. Other causes of death included severe infections (9% of total deaths) or thrombotic complications (8% of total deaths). In 20 patients, (5% of fatal events), the cause of death was apparently unrelated to Hodgkin's disease or to its possible complications.

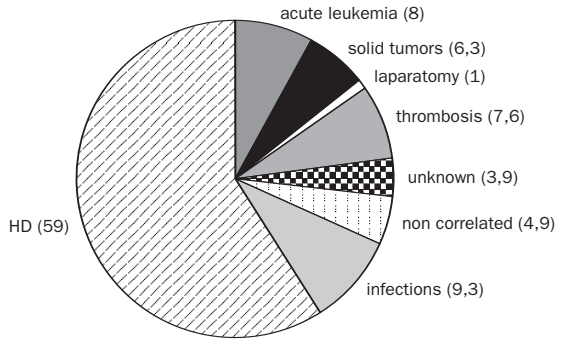

Figure 6. Causes of death for the entire cohort. Incidence was calculated on total number of dead (411 patients).

Discussion

This study on 1659 patients treated for Hodgkin's disease and regularly followed-up for a median time of 10 years has indicated a 4.2% long-term actuarial risk of developing a secondary acute leukemia (36 cases). In our experience, myelodysplasia preceded full-blown leukemia in all but one case; as previously emphasized,[27] a significant proportion of these secondary myelodysplasias consisted of isolated cytopenia, most frequently of the thrombopoietic line, with variable degrees of anemia and marked fibrosis at bone marrow examination.

We found no difference in the risk of subsequent leukemia according to the Hodgkin's disease status (complete remission or evidence of disease). The median time from the initiation of therapy for Hodgkin's disease to the diagnosis of secondary leukemia was comparable to that found after therapy with alkylating agents in other neoplasms such as non-Hodgkin's lymphoma,[45] polycythemia vera[46] and ovarian cancer;[47] the hazard function curve confirmed a substantial decline of risk of leukemia after the 10th year of follow-up, with no leukemic events beyond the 12th year.

The most important variables influencing the risk of subsequent leukemia were the type of therapy given for Hodgkin's disease and the class of drugs used. Patients who received radiotherapy alone, even on extended fields, demonstrated a very low risk of subsequent leukemia; the same held true for patients who had been given chemotherapy with no alkylating agents or procarbazine as for the ABVD regimen. At

variance, the risk of subsequent leukemia was substantial among patients given CT with alkylating agents and procarbazine as for the MOPP regimen; that risk was significantly higher among patients who received a combined modality therapy including total or subtotal nodal irradiation or radiation to the abdomen and pelvis and MOPP chemotherapy, either as adjuvant or salvage treatment.

Previous studies[12-15] and our own experience[4,18,27,48] have indicated a low risk of secondary leukemia in Hodgkin's disease treated with radiotherapy alone. Even though important evidence exists on the leukemogenic effects of ionizing radiations,[24,25] studies of cancer patients treated with high-dose RT generally did not find a substantial excess of subsequent leukemia.[49,50] Our findings confirm this observation; the situation in Hodgkin's disease is comparable to that of breast and cervical cancer where high-dose irradiation is given to small volumes of bone marrow; therefore, cell killing or cell inactivation predominates over cell transformation.

The substitution of MOPP with ABVD or ABVD-like regimens as first-line chemotherapy in Hodgkin's disease, has greatly reduced the overall risk of subsequent leukemia,[13,18,35] and has modified the relative incidence of this complication compared to other types of second malignancies, including non-Hodgkin's lymphoma and solid tumors.[35,48] In this study, we confirmed the absence of a long-term leukemogenic risk after the ABVD regimen, even when associated with RT. This can largely be attributed to the absence in the ABVD and ABVD-like regimens of alkylating agents and particularly of mechlorethamine and of procarbazine which have been conclusively demonstrated to be leukemogenic in animals.[22,23] A low incidence of secondary leukemia/myelodysplasia has recently been observed in a cohort of children with Hodgkin's disease treated with relatively low cumulative doses of alkylayting agents and no mechlorethamine.[51] In our experience, only one case of acute leukemia developed after ABVD and RT; the leukemia variant was of the promyelocytic type, as previously reported in detail.[52] This was very likely, however, a chance occurrence unrelated to prior therapy because of its peculiar cytology, the absence of a preleukemic phase and of all cytogenetic abnormalities which are considered as markers of therapy-related leukemia.[53,54]

The risk of subsequent acute leukemia was low even when ABVD was alternated with MOPP as front-line therapy. The alternating MOPP/ABVD program allowed overall administration of half the dose of alkylating agents and procarbazine compared to that given using the MOPP regimen alone; the lower total dose of alkylating agents accounts for the lower incidence of leukemia, since the leukemogenic risk of these drugs correlates with their cumulative dose, as demonstrated in different neoplasms.[34,55,56]

The statement that combined modality therapy produces a greater risk of leukemia than CT alone is still controversial. Large studies have demonstrated that one of the most significant factors for the development of leukemia in Hodgkin's disease is the combined use of radiation therapy and chemotherapy.[13,29,30,35] At variance, case-control studies failed to support this contention.[16,17,36] This study demonstrated, with both the actuarial and case-control analysis, a significantly higher risk of leukemia in the combined modality therapy group than in the CT alone group. In the setting of combined modality therapy, the major contribution to the risk of secondary leukemia derived from the use of MOPP chemotherapy and extended RT (total or subtotal nodal irradiation) including the abdomen and pelvis-Limited RT in addition to MOPP did not significantly increase the leukemogenic risk compared to that produced by MOPP chemotherapy alone; this observation is in line with the Yale experience,[28] suggesting that combination chemotherapy plus low-dose irradiation does not significantly increase the risk of developing second neoplasms above that reported for combination chemotherapy administered as either initial or salvage treatment.

Nitrosourea derivatives are known to be potentially leukemogenic in man.[57] In this study, an additive effect on the risk of leukemia, compared to that of MOPP alone, was observed when lomustine, a nitrosourea derivative, was used as part of a third-line conventional salvage therapy for recurrences after MOPP and ABVD; furthermore, the case-control analysis indicated that the use of lomustine was an independent risk factor. This finding is in keeping with the experience of the *British National Lymphoma Group*[16] in whose series most patients developing leukemia had received this drug. The recognition of a possible leukemogenic role of nitrosourea derivatives in clinical situations is of great relevance and, at least in part, can account for the cases of myelodysplasia and leukemia recently reported after autologous bone marrow or peripheral stem cell transplantation in lymphoid malignancies; in most of these cases, conditioning regimens including nitrosourea derivatives had been used.[58-60] In our series, most of the patients who received lomustine for multiple recurrences, were given etoposide in association, as well. Epipodophyllotoxin derivatives have recently been implicated in the development of leukemia in patients with germ-cell tumors[61] or in children treated for acute lymphoblastic leukemia.[62] This study indicated an increased risk of leukemia in patients treated with etoposide as part of their salvage therapy; it was impossible, however, to assess the independent effect of this drug on leukemia risk because, in most cases, etoposide was given in combination with lomustine which is known to be potentially leukemogenic, as well.

In our experience, the risk of secondary acute leukemia in Hodgkin's disease correlated with duration of chemotherapy; a significant cut-off was found

for an overall CT duration of 8 months which generally meant a cumulative eight cycles of therapy. In a large case-control study,[17] patients who had received more than six cycles with mechlorethamine-procarbazine (with or without radiotherapy) had a risk about three times higher than those treated with six cycles or fewer; likewise, in the *British Lymphoma Group* study,[16] the risk of leukemia increased with the amount of treatment, measured both by the number of cycles of alkylating agents and the number of attempts at treatment. All these experiences reinforce the concept of a cumulative leukemogenic effect of alkylating agents and procarbazine in Hodgkin's disease; this should caution for the shortest possible use of these drugs as front-line therapy and against their use as retreatment for relapses. This can also account for the substantial risk of leukemia we have found in patients who before 1981 received long-term maintenance therapy including alkylating agents

Splenectomy has been described as a covariate that influences the risk of acute leukemia and myelodysplasia in Hodgkin's disease.[17, 31] In a prior study on patients treated with MOPP and radiotherapy,[32] Cox's proportional hazards regression showed that splenectomy and the cumulative number of MOPP cycles (more than four) were the significant risk factors for acute leukemia. In the present study, splenectomy was not an independent variable for subsequent leukemia when evaluated in the whole series of patients; at variance, splenectomy status was influential among patients who had been given a combined modality therapy including MOPP regimen. Even in this group of patients, however, both case-control and actuarial analysis indicated that the risk created by MOPP chemotherapy significantly outweighed that conveyed by splenectomy *per se*. The effect of splenectomy was much reduced after adjustment for the number of cycles of CT including alkylating agents. The mechanism by which splenectomy can favor the development of second primary cancers in the setting of combined modality therapy including alkylating agents is unknown; hypothetically, a decreased immunosurveillance status induced by splenectomy may enhance a direct leukemogenic effect of the alkylating agents. On the other hand, in a recent study of second primary cancers in patients continuously disease-free from Hodgkin's disease,[33] both splenectomy and splenic irradiation correlated with the risk of secondary solid tumors, whereas the risk of acute leukemia or myelodysplasia was not increased. In conclusion, splenectomy can be considered a risk factor for leukemia in Hodgkin's disease only in particular settings of patients; its influence should be adjusted for type, intensity and duration of the overall therapy.

Previous studies have indicated that age at diagnosis[5-7] and advanced stage[17] may be independent variables for risk of leukemia in Hodgkin's disease; the cut-off for age was generally at 40 years and older patients were considered at increased risk. In this study, log-rank analysis indicated that age was of borderline significance with a critical cut-off at 30 years; case-control analysis did not show an independent effect of advanced age on risk of subsequent leukemia. Neither the *British National Lymphoma Group,*[16] nor a large international collaborative case-control study,[17] found that age influenced the risk of subsequent leukemia. Advanced stage was influential in the conditional logistic regression analysis; however, significance was not reached when the stage was adjusted for the type and duration of therapy.

The analysis of the causes of death and of their contribution to actuarial mortality can put the problem of secondary leukemia in Hodgkin's disease into the right perspective. Events related to the progression of disease are still the predominant causes of death in HD; therefore, the risk of subsequent leukemia must be weighed against the risk deriving from the lack of control of the primary neoplasm. In Hodgkin's disease, the gains of an effective therapy largely exceed the losses deriving from its toxicity; nonetheless, attempts should be made to reduce any iatrogenic risk further. As far as leukemogenic risk is concerned, the results of this study should indicate the opportuneness of reducing or abolishing alkylating agents and procarbazine from front-line regimens, of limiting combined modality therapy when alkylating agents are involved, and of avoiding nitrosourea derivatives in salvage therapy and in conditioning regimens for autologous bone marrow or peripheral blood stem cell transplantation. The observed cumulative effect of chemotherapy on the leukemia risk should prompt the adoption of the minimal therapy needed to cure Hodgkin's disease. In patients with early-stage disease, the use of short-term (three to four cycles) chemotherapy with no alkylating agents and limited-field radiotherapy can spare laparotomy and splenectomy and be equally curative and less toxic than RT with adjuvant MOPP.[63] In advanced stage disease, based on results of a large randomized study,[64] ABVD can effectively substitute MOPP or MOPP can be used alternating with ABVD. A significant reduction of leukemia risk is expected among patients treated in the last decade according to these general guidelines; avoiding this severe long-term iatrogenic complication will further improve the overall curability of Hodgkin's disease.

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EB and APA formulated the design of the study; EB wrote the paper and was responsible for the contact with participants. EB, APA, CK and MS were responsible for data handling and analysis; CK was responsible for statistical analysis and interpretation. CDB was responsible for the pathological review at the University "La Sapienza" of Rome. RME was responsible for radiotherapy at the University "La Sapienza" of Rome. CK illustrated the statistical methods in the "Statistics" paragraph of the "Materials and Methods" sec-

tion. All the authors critically revised and approved the final version of the paper.

Criteria for the authors name order: EB for study conception and formulation; for clinical work, data handling, analyzing and interpreting and paper writing; APA for clinical work, data handling, analyzing and interpreting; CK for statistical analysis and interpretation; MS for data handling; EO, GP, FL, ML for patient follow-up; RME for radiotherapy at University "La Sapienza" of Rome; CDB for pathology at University "La Sapienza" of Rome; FM and CB as Directors of the two partecipating Institutions.

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