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Risk of Leukemia in Patients Treated for Hodgkin's Disease

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Abstract—*We reviewed 251 consecutive adult patients with Hodgkin's disease treated at the Division of Hematology, Policlinico S. Matteo, Pavia, from January 1970 to December 1979, to assess the risk of development of acute leukemia. The median time of follow-up was 48 months (range 6–135). No leukemia occurred in 88 patients treated with radiotherapy or chemotherapy alone. Six acute non-lymphoid leukemias occurred in the group of 163 patients treated with MOPP and radiotherapy (crude rate of leukemia of 7.5 per 1000 person-years at risk). All cases were in clinical remission and off-therapy; the latent period from initiation of therapy to onset of leukemia ranged between 30 and 90 months. The actuarial probability of leukemia at five and seven years was 2.9 and 4.7% for the entire group of patients, and 3.8 and 5.8% for the combination therapy group. All leukemias, except one, had a preleukemic phase lasting 1–12 months, with cytopenia and dysplastic marrow. The median survival after leukemia was 4.7 months.*

INTRODUCTION

THE MORE aggressive therapeutical management of Hodgkin's disease (HD) in the last decade, with intensive radiotherapy (RT), combination chemotherapy (CT), and both modalities, had substantially improved the survival and the cure rate at almost any stage of Hodgkin's disease [1–5].

However, the concern about the long-term side effects of therapy is increasing, mainly due to the higher risk of developing second neoplasia and particularly acute non-lymphoid leukemia (ANLL), observed in patients treated with the combination modality approach [6–10].

The large majority of the patients developing leukemia in the recent reports were given total nodal or sub-total nodal irradiation and chemotherapy (adjuvant or salvage) with MOPP or MOPP-modified regimens, including alkylating agents and procarbazine; interestingly, no cases of leukemia or solid tumor occurred in a series from NCI of Milan, when the patients were given ABVD regimen in combination with RT [9].

In the present work we restricted the analysis of second malignancies to the cases of acute non-lymphoid leukemia (a) to assess the true risk of leukemia associated with different modes of treatment, and (b) to characterize the clinico-pathological features of secondary ANLL.

MATERIALS AND METHODS

The study includes 251 consecutive adult patients with biopsy-proven untreated Hodgkin's disease, admitted to the Division of Hematology, Policlinico S. Matteo, Pavia, from January 1970 to December 1979. Approximately 60% of patients were surgically staged; the staging was according to Ann Arbor classification [11]. The median time of follow-up was of 48 months, with a range from 6 to 135 months.

Table 1 gives the composition of the treatment groups as at December 1979.

RT alone was delivered as high-energy irradiation only to the patients in stage IA, and CT alone with MOPP regimen as primary treatment to the patients with stage IV. Patients in stages IIA, IIIA, IIB, IIIB were treated with a combination of high-energy RT and chemotherapy, with MOPP regimen as adjuvant (stages IIA and IIIA), or in a 'sandwich' sequence (stages IIB and IIIB). A fraction of the patients in stage IIIB without 'bulky disease' were treated with CT alone. ABVD [12] or

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Table 1. Treatment groups

Treatment	No. of patients
Radiotherapy alone	
Total nodal irradiation	14
Subtotal nodal irradiation	4
Total	18
Chemotherapy alone	
MOPP	45
MOPP + ABVD	17
MOPP + CCNU	8
Total	70
Combined modality	
Total nodal irradiation + MOPP	63
Total nodal irradiation + MOPP + ABVD	34
Limited field* + MOPP	63
Limited field + procarbazine	3
Total	163

*Limited field is defined as radiation therapy on one side of the diaphragm.

different regimens, including nitrosoureas, were given only as salvage treatment at any stage.

The cumulative time-risk of developing leukemia was defined as person–years at risk, calculated for the whole series or separately for each group of treatment, and the observed leukemia was defined as person-years at risk, ANLL per 1000 person-years at risk. The actuarial risk of secondary leukemia was calculated from the date of initial treatment using the life-table method.

The leukemias were classified according to the criteria of the French–American–British (FAB) classification [13].

Terminal transferase assay was done as previously described [14].

RESULTS

Table 2 gives the crude rate of acute leukemia in the given period of observation for the study population. No cases of leukemia were observed among the 88 patients given RT or CT alone. Six cases of acute non-lymphoid leukemia were seen in the group of 163 patients treated with combination therapy, with a crude rate of 7.5 ANLL per 1000 person-years at risk.

The type of treatment given to the six patients who subsequently developed ANLL and the latent periods from the beginning and the end of treatment are shown in Table 3. Four of the six patients were given extensive radiotherapy and combination chemotherapy with MOPP; the other two cases were given limited field irradiation followed by MOPP and procarbazine, in monochemotherapy as adjuvant, respectively. The overall duration of therapy was variable and ranged from 11 to 63 months; five patients were in their first clinical remission from Hodgkin's disease and off-therapy while developing ANLL, and the other single case was in the second complete remission and had been given MOPP as salvage treatment for twelve months. The sequence of treatment was RT followed by CT in two cases, and CT followed by RT in four cases (two cases with 'sandwich' sequence CT–RT–CT). The median time of latency from the beginning of therapy and the diagnosis of leukemia was of 41 months (range: 30–90) and from the end of therapy to ANLL was of 23 months (range: 13–31).

The mean actuarial risk of development of acute leukemia at five and seven years after the initiation of therapy for Hodgkin's disease was 3.8 and 5.8% among the patients who had received combined radiotherapy and chemotherapy, and 2.9 and 4.7% for the entire study population.

The characteristics and the clinical course of leukemia are summarized in Table 4. All leukemias except one had a 'preleukemic' phase lasting 1–12 months, and the mor-

Table 2. Crude rate of acute leukemia in the study population

Treatment	No. patients	Median follow-up (months)	Range (months)	No. leukemia/ No. person-years at risk	Crude rate of ANLL per 1000 person-years at risk
RT only	18	26	15–81	0/50.2	0.0
CT only	70	30	6–135	0/236.5	0.0
Combined modality	163	48	6–135	6/786.5	7.5
Whole group	251	48	6–135	6/1073.0	5.6

RT = Radiotherapy; CT = chemotherapy; ANLL = acute non-lymphoid leukemia.

Table 3. Type of treatment given to patients developing leukemia

Treatment	No. of leukemia	Sequence of treatment	Time to diagnosis of leukemia (months) After beginning of treatment	After end of all treatment
Total nodal irradiation + MOPP	4	CT + RT	32	21
		CT + RT	38	25
		CT + RT + CT	90	27
		RT + CT	72	31
Upper mantle irradiation + MOPP	1	CT + RT + CT	44	13
Inverted Y irradiation + procarbazine	1	RT + CT	30	15

Table 4. Characteristics and course of leukemia

Case	FAB classification	Preleukemia phase	TdT assay	Therapy	Response to therapy	Survival from HD diagnosis	Survival from ANLL diagnosis
1	M_0	yes	negative	DR, CA	CR	101+	9+
2	M_3	no	negative	DR	CR	37+	3+
3	M_4	yes	negative	COAP, VP16213	PR	85+	11+
4	M_4	yes	nd	supportive	—	48	2
5	M_4	yes	nd	supportive	—	45	5
6	M_{5a}	yes	nd	POMP	NR	36	5

DR = Daunorubicin; COAP = cyclophosphamide, oncovin, cytosine arabinoside, prednisone; POMP = 6-mercaptopurine, oncovin, methotrexate, prednisone; CA = cytosine arabinoside; CR = complete remission; PR = partial response; NR = no response; nd = not determined.

phology of overt leukemia was myelomonocytic in three cases, monocytic poorly differentiated, promyelocytic and unclassifiable, respectively, in the other three cases. Mononuclear cells separated from three cases were tested for the presence of the enzyme terminal transferase. All cases were negative and the test was particularly useful in the case of unclassifiable leukemia, who, after therapy with daunorubicin and cytosine arabinoside, achieved a complete hematological remission. The response to therapy of all patients, and the survival times from diagnosis of HD and ANLL, respectively, are reported in Table 4. The median survival from diagnosis of Hodgkin's disease was of 46 months (range: 36–101+), and from ANLL, 4.7 months (range: 2–11+).

Detailed information concerning the

preleukemic phase is given in Table 5. Anemia, with anisocytosis, prominent macrocytosis, basophylic stippling and circulating erythroblasts, was a characteristic hematological feature in all cases. Granulocytic abnormalities consisted of defect of granulation, decrease or absent myeloperoxidase activity and Pelger–Huet anomalies. All cases exhibited thrombocytopenia with megathrombocytes; in two cases, circulating micromegakaryocytes were present. Bone marrow biopsies and aspirates were hypocellular, with abnormalities of all the maturation lines: megaloblastoid features with multinuclearity of erythroblasts and occasionally sideroblasts, moderate excess of blasts and promyelocytes, increased percentage of monoblasts and monocytes, and presence of 'paramyeloid cells' and micromegakaryocytes.

DISCUSSION

In our series of 251 patients with Hodgkin's disease, the crude rate of ANLL was 7.5 per 1000 person-years at risk for the combined modality treatment group. This crude rate of ANLL is comparable to those reported by various major institutions after 1970, as recently reviewed [15], and is an approximation of the average annual incidence of ANLL in HD.

The actuarial risk of ANLL at five and seven years for the entire group of patients and for the combination therapy group is similar to those from all other reports using the life-table analysis [7, 9, 10, 16]. All patients developing acute leukemia in our series were in clinical complete remission and were given an RT and MOPP regimen (five cases), or procarbazine in monochemotherapy (one case). Of interest, two of the six patients were given only a limited field radiotherapy, followed by MOPP and procarbazine respectively. These data confirm that a combined modality approach to therapy of HD, in particular if it includes the administration of procarbazine and alkylating agents, is somehow related to the development of subsequent ANLL. We suggest a possible direct leukemogenic role of this particular form of treatment; this conclusion has already been stressed by Valagussa from NCI of Milan [9], who reported the occurrence of acute leukemia after treatment with MOPP or modified MOPP regimens, and no cases of leukemia in patients given ABVD at comparable times after primary treatment.

Table 5. Hematological data at time of diagnosis of preleukemia

	Case				
	1	3	4	5	6
Peripheral blood					
Hemoglobin (g/dl)	8.1	10.2	7.8	10.8	6.7
Mean corpuscular volume (μm^3)	113.0	108.0	121.0	109.0	111.0
Anisocytosis	+	+	+	+	+
Basophilic stippling	+	+	+	+	+
Erythroblasts (× 100 WBC)	13.0	12.0	14.0	27.0	10.0
WBC ($\times 10^9$/l)	3.5	10.5	7.3	4.6	3.2
Monocytes ($\times 10^9$/l)	0.3	1.2	1.2	1.0	0.9
Blast cells (%)	0.0	12.0	21.0	0.0	8.0
Hypogranularity in PMNC	+	+	+	+	+
Pelger–Huet	+	+	+	+	+
Platelets ($\times 10^9$/l)	120.0	60.0	90.0	100.0	70.0
Megathrombocytes	+	+	+	+	+
Micromegakaryocytes (× 100 WBC)	0.0	5.0	3.0	0.0	0.0
Paramyeloid cells	+	+	+	+	+
Bone marrow					
Hypoplasia	+	+	+	+	+
Fibrosis	−	−	+	−	+
Myeloid—erythroid ratio	3 : 1	4 : 1	4 : 1	3 : 1	3 : 1
Blast cells (%)	3.0	35.0	40.0	35.0	15.0
Dyserythropoiesis	+	+	+	+	+
Micromegakaryocytes (× 100 WBC)	5.0	10.0	8.0	0.0	3.0

WBC = White blood cells; PMNC = polymorphonucleated cells.

All cases of acute leukemia, we observed, were of non-lymphoid type, and presented as a clinically distinct hematological entity, different from *de novo* ANLL. Five out of six cases were heralded by prolonged periods of macrocytic anemia, with circulating erythroblasts, thrombocytopenia, monocytosis in peripheral blood and dysplastic features with excess of blasts in bone marrow. These morphological characteristics were closely resembling a chronic myelomonocytic leukemia. The terminal leukemic phase was of monocytic or myelomonocytic type. The involvement of the monocytic line in ANLL developing after therapy for Hodgkin's disease was reported by others and substantiated by the multiple cell markers analysis [17]. It has been proposed that the acute leukemia occurring in Hodgkin's disease may represent a malignant progression of the original disease [18]; in our cases, nevertheless, the remission status of Hodgkin's disease and the latent period from institution of therapy to development of ANLL should permit us to rule out this eventuality.

In almost all reports, the leukemia was considerably more refractory to antileukemic therapy, with only 6.5% of the patients entering complete remission [19]. In our experience, however, two of the four patients who were given adequate chemotherapy with daunorubicin and cytosine arabinoside achieved a prolonged complete remission.

There is, now, a trend toward the use of combined modality therapy to improve the cure rate for all stages in Hodgkin's disease. However, the observed higher risk of developing subsequent leukemia in patients treated with this mode of treatment should be carefully considered in planning the future therapeutical protocols. In particular, the patients with disease limited to one side of the diaphragm without systemic symptoms should be treated with radiotherapy only, without adjuvant chemotherapy, or, conversely, the patients with systemic symptoms without 'bulky disease' should be treated at any stage with chemotherapy alone. The combined modality of treatment in our program will be employed in stage IIIA (CT as adjuvant to RT), and in stages IIB and IIIB with nodular sclerosis histology and bulky mediastinum.

Concerning the type of chemotherapy, the possibility of using an alternative scheme as effective as MOPP without procarbazine and alkylating agents as primary treatment in Hodgkin's disease will be considered, to reduce the leukemogenic risk.

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