POST-THERAPEUTIC ACUTE LEUKEMIA

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This study reports 35 cases of posttherapeutic acute leukemia and reviews the literature on this subject. These AL's are characterized by a high incidence of anemia, in particular refractory anemia, preceding the hematological disorder by several months, by the frequent finding of myelofibrosis, by the essentially granulocytic nature of the AL, and by the low rate of remission and the, in general, extremely short survival of a few months. These leukemias may develop following continuous chemotherapy with an alkylating agent, radiotherapy of various extent, or most commonly following intensive treatment with extensive irradiation and polychemotherapy as in the management of Hodgkin's disease. In view of these therapeutic hazards, the present objectives are the modification of alkylating agent therapy by the use of other drugs and sequential administration, and a reduction in the dose and field of irradiation and the duration of polychemotherapy, as in Hodgkin's disease; all present protocols are orientated in this direction.

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This article is a report of 35 cases of acute leukemia developing posttherapeutically which have been observed on the service of Professor Jean Bernard in the last 20 years. In 60% of these cases, the leukemia developed following Hodgkin's disease; in the other cases, the initial disorders were: 4 cases of myeloma, 1 case of chronic lymphocytic leukemia (CLL), 1 case of rheumatoid arthritis (RA), 1 nephrotic syndrome and 7 solid tumors (5 cases of carcinoma of the breast, 1 testicular seminoma and 1 endometrial adenocarcinoma). In these 35 cases the leukemia was essentially granulocytic and survival, in general, was of a few months duration.

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Over the past 10 years, reports have appeared regularly and fairly frequently in the literature noting the association between acute leukemia and other disorders in which the majority of patients received treatment with either immunosuppressive agents or radiotherapy. The disorders noted to precede the acute leukemia have been extremely varied. However, as in our series, certain hematological disorders are prominent: multiple myeloma, chronic lymphocytic leukemia and Hodgkin's disease, as also are cancer of the breast and the ovary.

Observations

Acute Leukemia and Multiple Myeloma

Four cases of myeloma followed by the development of an acute leukemia were observed (Table 1). All were treated with Melphalan for a period of three years and none presented any particular points (except for case number 1 who demonstrated an isolated plasmacytoma of the cavum irradiated initially with a dose of 4500 rads). One point of note, however, is that all experienced a survival of greater than 4 years.

In addition, in case number 2, the development of an anemia was detected more than one year prior to the leukemia and in the following patient, a myelofibrosis suggested the possibility of an acute transformation of a chronic myeloid leukemia, but the L.A.P.

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TABLE I. Chemotherapy and Acute Leukemia

Myeloma				
1 PAR M 37 M	3.65: plasmacytoma (cavum)—cobalt (4500 r) 3.70: MELPHALAN × 3.5 years		12.73: AML	Remission Survival—10 months
2 DUA T 65 F	2.69: MELPHALAN × 6.5 years	9.74: anemia	12.75: Idio. Thrombocyth.	Failure Survival 1 month
2 ALY G 72 M	1970: MELPHALAN × 4 years	6.74: medullary fibrosis	7.74: Oligo. L or AT CML	Survival 1 month
4 LAM C 76 F	6.70: MELPHALAN × 7 years	—	6.77: Oligo. L	Living
C.L.L.				
5 CAN L 70 M	11.69: CHLORAM. × 7.5 years	—	3.77: AML	Failure Survival less than one month
R.A.				
6 MON N 52 F	1972: CHLORAM. × 2 years	2.77: CBC normal 3.77: anemia	5.77: AML	Remission Survival 1 month (Died hepatic-steatosis)
Nephrotic syndrome*				
7 JAC C 52 F	1967: AZATHIO. × 2 years + CHLORAM. × 3 years		4.74: AML	Failure Survival 1 month

* Patient of Professors Dreyfus and Lagrue (Hospital Henri-Mondor).

was normal and the Philadelphia chromosome was absent. However, chromosomal studies demonstrated a type C deletion. The prognosis of these leukemias was extremely poor.

Acute Leukemia and Chronic Lymphocytic Leukemia

Out of more than 400 cases of CLL followed on the service, one case (number 5) receiving a continuous therapy with Chlorambucil for more than 7 years, eventually developed an acute myeloblastic leukemia (AML). Here again, survival was short.

Acute Leukemia and Rheumatoid Arthritis

This patient (case number 6), following the failure of gold therapy, was commenced on Chlorambucil for a period of two years for his R.A. which was considerably ameliorated. Anemia developed three years following the cessation of his chemotherapy and was followed two months later by an acute myeloblastic leukemia. The bone marrow biopsy which was performed demonstrated massive blastic infiltration but no fibrosis. Therapy induced a remission but the patient died one month later, abruptly, from hepatic steatosis.

Acute Leukemia and the Nephrotic Syndrome

In 1966, a 56-year-old female (case number 7) developed the nephrotic syndrome, confirmed by renal biopsy in 1967 (stage 3). Azathioprine therapy was commenced, but after 15 months, it was replaced by Chlorambucil which was continued until January 1973. One year later, a blood count showed 9700 leucocytes of which 83% were myeloblasts; the bone marrow confirmed the diagnosis and the patient died within the month despite antileukemic therapy.

Acute Leukemia and Cancer

In 5 cases (cases numbers 8 to 12), cancer of the breast preceded an acute leukemia by three to sixteen years (Table 2). One patient was treated only with surgery, the other four receiving radiotherapy of at least 3000 rads. In two patients (cases numbers 8 and 10), anemia developed several months or years before the acute leukemia. In the two patients in whom a bone marrow biopsy was performed at the onset of the leukemia a diffuse fibrosis was noted. Only the patient not having received radiotherapy had a survival of

greater than 1 year. Another case (case number 13) concerned a 67-year-old male, treated in 1970 for a seminoma of the left testicle by orchidectomy and subdiaphragmatic and mediastinal radiotherapy. In July 1971, he was commenced on a combined chemotherapeutic regimen including an alkylating agent for three years. In May 1974, the development of anemia necessitated blood transfusion until May 1976 when the acute myeloid leukemia appeared. The patient died during the following month.

Case number 14 concerns a 51-year-old female who in 1971 underwent a hysterectomy for endometrial adenocarcinoma, followed by pelvic radiotherapy with a dose of 6500 rads over three months. In March 1975, a pancytopenia developed; the bone marrow biopsy performed one month later revealed an acute undifferentiated leukemia. Despite intensive chemotherapy, the patient emerged from a long period of aplasia with blasts still present and died in June 1975.

Acute Leukemia and Hodgkin's Disease

At the present time, 21 cases of secondary acute leukemia have been observed out of more than 2000 patients with Hodgkin's disease treated on the service from 1957 to 1977 but only 1150 were alive after 2 years (450 of them were treated by radiotherapy alone, 300 by chemotherapy alone and 400 by chemotherapy followed by radiotherapy). Certain of these have formed the basis of previous publications (18 to 19). Table 3 summarizes the principal characteristics of these cases of Hodgkin's disease. The mean age was 37 years, 9 patients being female and 12 male. The initial anatomical stage was stage I in 7 cases, stage II in 6 cases, stage III in 6 cases and stage IV in 2 cases. The interval between the two disorders was a mean of 7.5 years ranging from 2 to 11.5 years.

Treatment had generally been intensive, comprising either extensive radiotherapy (3 cases), combined chemotherapy (9 cases) or the combination of these two approaches (7 cases); only two patients were treated by local irradiation and single agent chemotherapy. Alkylating agents were used in 15 patients within a protocol comprising several drugs or alone as maintenance therapy, and 6 patients received supra and sub-diaphragmatic radiation. The majority (17 cases) of cases of Hodgkin's disease were in remission at the time of development of the acute leukemia, 12 of them having been under treatment for several years. Table 4 demonstrates the characteristics of these secondary leukemias. They were often preceded by a cytopenia affecting essentially the erythroid elements, but also platelets and in one third of cases the leucocytes. When a bone marrow biopsy was performed at the time of the leukemia, in addition to profound hypoplasia a diffuse myelofibrosis was frequently found. These secondary acute leukemias were essentially myeloblastic (17 cases), more rarely lymphoblastic (3 cases) and in 1 case promyelocytic. Despite anti-leukemic therapy, the results were disappointing with 15 total failures; two of the three A.L.L. went into remission but survival was very short, a mean of two months; only 5 patients lived longer than ten months and only one is still living but with a relapse of his AML. Although the majority of patients

TABLE 2. Cancer of the Breast and Acute Leukemia

Irradiation								
8	PLI	M.A.	70 F	1951:	>3000 r	3.77: anemia	6.77: Oligo. L	Alive
9	MAL	L.	57 F	1962:	>3000 r	—	3.76: AML	Failure Survival 2 m.
10	GOU	M.	52 F	1966:	6500 r	7.71: macrocyt. anemia 1972: intra-medul. hemolysis 4.76: medul fibrosis	4.76: AL, micromega-karyocyt.	Failure Survival less than 1 month
11	CAZ	L.	64 F	1973:	6000 r	1.76: medul fibrosis	1.76: AML	Failure Survival 3 months
No radiation								
12	LAD	G.	71 F	1969:	Halsted	—	10.74: Acute mono. L.	Remission Survival 14 months.

TABLE 3. Hodgkin's Disease Complicated by Acute Leukemia: 21 Cases

			Onset	Treatment	Interval	Actual status
1	CAT	22 F	1956: IA	*,‡	8 years	2d CR
2	MOR	26 F	1961: IIIB	*,‖,§	8	2d CR
3	KLE	23 F	1962: IIIAb	*,†,§	7	4th CR
4	VAN	42 F	1962: IIA	*,‖,†,§	7	3rd PR
5	LEL	60 F	1962: IIAa	‖,*,‖	11	2d CR
6	DEC	31 F	1963: IIAa	*,§	8	2d CR
7	VAN	23 F	1961: IVAb	*,§	9	4th Relapse
8	MAR	54 M	1967: IAa	†,‖	6	1st CR
9	YZO	73 M	1971: IIIBb	§,‡	4	1st CR
10	ROM	16 F	1965: IIAa	†,‖	9	1st CR
11	CAR	30 M	1963: IIAa	*,§	11.5	3rd Relapse
12	DUP	25 M	1965: IAa	†,§	11	3rd Relapse
13	MON	50 M	1949: IAa	*,§,‖	8	2d CR
14	BEN	35 F	1969: IIIBb	§	8	1st CR
15	FOU	30 F	1971: IIIBb	§,‖	6	1st CR
16	MON	36 M	1972: IVBb	§,‖	3.5	2d CR
17	DEN	20 M	1972: IAa	§,†	2	1st CR
18	CAZ	5 M	1962: IIAa	†,‖,§	5	2d CR
19	LEG	8 M	1969: IAa	†,‖	7.5	2d Relapse
20	PET	33 M	1975: IAa	§,†	2.5	1st CR
21	FAV	60 M	1966: IIIBb	†,‖,§	9.5	3d PR

* Local radiotherapy.
† Extended radiotherapy (mantle or inverted Y).
‡ Monochemo.
§ Polychemo.
‖ Alkylating agent.
C.R.: complete remission; P.R.: partial remission.

underwent one or more relapses in the evolution of the Hodgkin's disease, four were patients with stage I Aa and II Aa who were treated in two cases only by extensive radiation followed by maintenance therapy (one with Chlorambucil, the other with Vincaleucoblastine) for three years, the other two patients receiving three courses of MOPP therapy followed by mantle radiation.

REVIEW OF THE LITERATURE

Acute Leukemia and Hematological Disease

In 1966, in a review of 310 cases of multiple myeloma,[35] Nordenson concluded that a leukemia developed in 7% of the cases and he reported five cases of ALL and two of AML, without specifying the evolution.

The following year, a new case of AML was published[11] following which further examples of this association were reported regularly.[1,17]

In 1974, Rosner published 12 personally observed cases[38] and reviewed 46 cases described in the literature. Except for the publication of Nordensen, all were acute granulocytic leukemias, and, although in five cases the diagnosis of the two disorders was made simultaneously, the majority of the other cases of myeloma had received Melphalan therapy for several years.

The same year, Karchmer[22] reported five other cases against an expected incidence of 0.17 and Turz[53] described two cases of the simultaneous development of the myeloma and AML, preceded by a severe pancytopenia of several months duration, with a two month survival.

In the last two years, a number of publications[8,12,27,29,34] have documented the development of a refractory anemia with partial myeloblastosis secondary to multiple myeloma treated with Melphalan, this refractory anemia terminating in AML. The bone marrow suppression due to therapy and the evolution of the myeloma may perhaps be a contributing factor; however, the simultaneous appearance of the two disorders prior to the administration of any therapy suggests that the leukemia may be a development of the myeloma enhanced by the intrinsic immunosuppression of the disorder. The prolonged therapy accentuates the immunosuppression and the secondary leukemia may only appear after several years of treatment, the risk thus increasing with the duration of survival.

Acute leukemia may similarly complicate other hematological disorders, such as Waldenström's macroglobulinemia,[30,38] in four cases treated by alkylating agents, in three cases the two disorders appearing

simultaneously. The development of AML in three cases of lymphoma treated with Chlorambucil[15,50] and in two patients treated for amyloidosis,[26] and of erythroleukemia in a patient treated with Melphalan for cold agglutinin disease[49] have similarly been reported.

Zarrabi, in 1977,[40] in a review of the literature encompassing 1354 cases of chronic lymphocytic leukemia (CLL) found 40 cases of acute leukemia of which 9 were ALL, four of these being diagnosed at the same time as the CLL.

The patients were treated with either radioactive phosphorus or radiotherapy, chemotherapy, or a combination of these diverse therapies. The mean interval between the two disorders was five years.

Acute Leukemia and Cancer

The use of alkylating agents in the treatment of advanced cancer appears to increase the frequency of secondary AL; numerous cases have been reported in cancer of the ovary,[23,24] and also of the lung,[13,47] and brain[5] in one case of malignant melanoma and in one case of cancer of the bladder treated with intravesicular Thiotepa. Cancer of the breast is rather special in view of the increased frequency of AL even in the absence of any complementary therapy.[4] Nonetheless, numerous cases have been described following chemotherapy with alkylating agents.[9]

With regard to cancer of the ovary, Reimer[37] found 13 cases of posttherapeutic acute leukemia (9 AML, 3 erythroleukemias and 1 acute myelomonocytic leukemia) among 4324 patients followed in 70 centers between 1970 and 1975. These 13 cases had been treated for more than 1 year (mean of 24 months). The interval between the two disorders was 42 months (from 30 to 90 months) and an unexplained pancytopenia preceded the AL by 1 to 12 months (mean 6 months) in 9 of the 13 cases. Following the diagnosis of the leukemia, the survival was short, with a median of 1.5 months.

Other cancers present the same characteristics, with anemia preceding the granulocytic leukemia by several months.

The development of acute leukemia following cancer of the breast is fairly frequent since Carey in 1967[4] reported 6 cases of AML in patients treated by surgery alone (30 times the theoretically predicted number considering the relative frequency of the two dis-

TABLE 4. Hodgkin's Disease Complicated by Acute Leukemia

	CBC (Greater than 3 months prior to AL)	BM	Type	Result	Survival
1	RBC↘	hypopl + fib.	AML	CR	10 m
2	ND	ND	AML	Failure	1
3	pl↘	ND	AML	Failure	1
4	ND	ND	ALL	Failure	2
5	ND	aplasia	AML	Failure	1
6	RBC↘WBC↘	ND	AML	Failure	3
7	RBC↘	hypopl	AML	Failure	1
8	RBC↘WBC↘ pl↘	fibrosis	AML	Failure	1
9	ND	ND	AML	Failure	1
10	RBC↘ pl↘	ND	AML	Failure	2
11	RBC↘ pl↘	ND	AML	Failure	1
12	WBC↘ pl↘	ND	AML	Failure	1 wk.
13	ND	ND	AML	Failure	1
14	RBC↘	ND	AML	Failure	1
15	RBC↘WBC↘ pl↘	ND	AML	Failure	3
16	RBC↘ pl↘	hypopl	AML	CR	13 + (REL)*
17	NORMAL	ND	ALL	CR	10
18	NORMAL	ND	ALL	CR	12
19	RBC↘ pl↘	ND	AML	Failure	1
20	ND	ND	APL	In process	1
21	WBC↘	ND	AML	CR	15†
			17 AML 3 ALL 1 APL	15 failures 5 CR 1 in process	5 pts. > 10 mos.

ND = not done.
* REL = relapse. Patient followed by Professor Hollard (Grenoble).
† Patient followed by Professor Tanzer (Poitiers).

orders) and 20 cases of AML in those treated with surgery followed by radiotherapy, which corresponds in this study to a frequency practically identical to that of patients treated by surgery alone. Rosner in 1978,[41] in a review of the literature (54 cases) and 24 personal cases reported 8 patients with the two diseases occurred simultaneously and 7 patients without radiotherapy or chemotherapy; the other patients received radiotherapy (but 8 received chemotherapy). Rosner observed that acute leukemia occurred with a sevenfold increased frequency over the expected number.

Acute Leukemia and Nonmalignant Disorders

Numerous nonmalignant disorders are treated by alkylating agents of immunosuppressive drugs, in particular rheumatoid arthritis and renal transplants. Over several years, numerous cases of acute posttherapeutic leukemia have been reported.[10,14,25,33,38,44,45,48,51,52] Recently, Louie[31] collected 31 such associations. 109 nonmalignant diseases were treated by immunosuppressive drugs and 94 received no treatment. Acute myelogenous leukemia (AML) or its variants were observed in 28 treated patients (25.9%) whereas only 2 AML in the untreated patients (3.2%); this difference is very significant and this apparently high proportion of AML in treated patients seems real. The interval between the two disorders varied from 2 to 20 years in treated patients and was 5 years in untreated group. It was also observed in two acute lymphoblastic leukemias in treated and untreated patients, but in the treated group their prognosis was equally as poor as that of the AML.

Acute Leukemia Following Radiotherapy

Numerous forms of cancer or benign disorders are treated by radiotherapy alone. Several cases of acute secondary leukemia have been reported, occurring in four cases of Wilms' tumor,[43] one cancer of the tongue,[36] five cases of cancer of the larynx;[21] all these patients had received local radiotherapy exceeding 3000 rads; in 7 cases the acute leukemia was myeloblastic and in the three others lymphoblastic. Survival was always less than 6 months. Similarly, one case of lymphosarcoma treated by radiotherapy alone was complicated by AML.[36] In a study of pelvic irradiation, Smith[46] documented 34 cases of acute leukemia (against a theoretically predicted number of 33) out of 110,000 cervical cancers treated locally by radium or by local radiotherapy (doses of 200 to 1500 rads). In contradistinction, in the same study, out of more than 8000 women in whom the menopause was induced by radiotherapy, (a dose of 70 to 190 rads to the entire pelvis), 33 acute leukemias developed while the theoretically predicted number was 13.5, almost threefold greater than the calculated incidence. In the same setting, approximately 15,000 patients with ankylosing spondylitis received radiation[6] and 60 of them developed leukemia (+16 cases of refractory anemia) whereas normally 6.8 patients would have been expected to present spontaneously with leukemia.

Acute Leukemia and Hodgkin's Disease

In 1969, Crosby[7] estimated that in patients with Hodgkin's disease treated with radiotherapy, the risk of a secondary AML was 10 times greater than in the general population.

In 1972, Arseneau[2] showed that the risk of developing a malignant tumor is a function of the intensity of treatment of the Hodgkin's disease and that this risk is maximal when extensive irradiation is combined with polychemotherapy since, in this situation, the frequency of post therapeutic AL is 29 times that of the general population. In a previous study[18] we had arrived at the same conclusion. In this study, taking into consideration the retrospect and the number of cases of Hodgkin's disease treated, we should have noted 0.28 cases of AML whereas 17 presented, the risk thus being approximately 60-fold that of the general population; if all acute leukemias are considered, the risk of the patient suffering from Hodgkin's disease and treated by present therapeutic modalities developing a secondary AL is 38 times greater than that of the spontaneous appearance of AL in the general population. With regard to the four most extensive reviews of the literature, Sahakian in 1974[42] reported 22 cases and Larsen in 1977[28] 21 cases, *i.e.*, a total of 43 acute leukemias; Rosner in 1975[39] and Cadman in 1977[3] in reviews of the literature reported 93 cases of acute leukemia and 109 cases of acute non lymphocytic leukemias, occuring subsequent to Hodgkin's disease. The same characteristics were found as in our

21 patients; the mean age, 37 years is less than of primary granulocytic leukemia, there was no difference in frequency between the sexes, and the mean interval between the two disorders was 5 or 6 years, but 7 patients were treated by chemotherapy alone and they developed acute leukemia earlier after diagnosis of Hodgkin's disease than did the other patients treated by radiotherapy, their median latent period was only 1.5 years. Rosner reported also 3 cases where the two diseases occurred simultaneously or within 6 months of each other and hence, coexisted. The majority of patients received radiotherapy (but in contrast 56 were never treated chemotherapeutically). The AL was generally granulocytic (only 11 ALL, in 4 of them, the two diseases occurred simultaneously), treatment was disappointing and survival never exceeded 6 months with a mean of one month. Grant in 1975[16] reported the reverse of these observations: an adolescent of 17 years with ALL in whom remission was induced and who, 15 months later, developed stage IV Hodgkin's disease.

DISCUSSION

Prior to the last 10 years, few cases of acute posttherapeutic leukemia were reported, but the initial malignances were often rapidly fatal and their treatment, in general, less intense than at the present time, extensive radiation and polychemotherapy having existed for only about the last 15 years. Alkylating agents certainly appear to play a contributary role, as illustrated by the study of Reimer where cancer of the ovary treated by alkylating agents resulted in a 36-fold increase in secondary AL (13 cases observed compared with a theoretically predicted number of 0.36) compared with the general population. In contrast, out of 6596 cases of cancer of the ovary treated with radiotherapy, the number of cases of AL observed was identical to that predicted, considering the relative frequency of these two disorders. The only difference between these two groups being the use of alkylating agents (9 of the 13 AL also received radiotherapy), it is logical to consider that these influence the frequency of post therapeutic AL, whether in cancer of the ovary or in other disorders treated by these agents such as myeloma or CLL. These chemotherapeutic agents probably exert their effect by accentuating the immunosuppression and generating chromosomal damage, as animal studies of Melphalan have demonstrated.[54] The mode of administration also plays a role, Jensen[20] having shown that although azatioprine administered continuously produces chromosomal abnormalities, when this treatment is stopped or converted to sequential administration the abnormalities disappear. The primary disorder may also have bearing on the development of secondary AL by virtue of the increase in survival time in disorders such as myeloma where the AL may be a terminal development as in the myeloproliferative disorders.

The association between cancer of the breast and AL also presents the problem of the role of the primary disorder, since in cancer of the breast treated by surgery alone, the risk of a secondary AL is 30 times that of the general population according to the study of Carey[4]: this raises the question of a possible common etiological mechanism, particularly in view of the fact that in Wistar rats the intraperitoneal injection of methylcholanthrene produces randomly either an AL or cancer of the breast, resembling closely the model of acute myelomonocytic leukemia in the Balb/C mouse established by Metcalf;[32] AL is produced in this case by the intraperitoneal injection of mineral oil; in other strains of mice this injection gives rise to a myeloma.

Radiotherapy appears to intervene more by virtue of the extent of the irradiation than the dose delivered, since irradiation of the pelvis with less than 200 rads multiplies by a factor of 3 the risk of AL, while 300 to 1500 rads to the cervis does not increase the frequency. The same is found in Hodgkin's disease, where extensive irradiation increases the incidence of post-therapeutic AL. In our study, six patients had received both supra and sub diaphragmatic irradiation. It is also possible that low doses result in cellular alterations within the chromosome without destroying the cell, which may thus multiply, these chromosomal abnormalities being in part responsible for the AL.

A number of factors may thus be postulated as intervening in the development of post-therapeutic AL, comprising the increase in survival time related to improvements in therapy, the genetic, viral and immunological aspects of the primary disorder and finally the chromosomal abnormalities and immunosuppression related to the treatment.

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