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ıuence of a Treatment Dose Response in Acute Nonlymphocytic eukemias Which Occur after Therapy of Non-Hodgkin's ymphoma[1]

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BSTRACT

'Ne evaluated the occurrence of second cancers among 517 atients with non-Hodgkin's lymphoma (NHL) treated at the lational Cancer Institute. Nine cases of acute nonlymphocytic eukemia (ANL) were observed compared to 0.08 cases expected (ratio of observed to expected cases, 105; 95% confidence limits. 48;199). The excess risk of ANL was 4.1 cases per 1000 patients per year: the cumulative risk of ANL at 10 years was 7.9 ± 3.2% (S.E.). A case-control study within the NHL cohort revealed that patients treated with both radiation and chemotherapy were at greater risk of ANL than were patients who received single-modality therapy (relative risk, 6.0: $p < 0.05$). especially if the therapy included total-body or hemibody radiation.

A positive correlation between cumulative radiation dose to t ne marrow and risk of ANL was demonstrated, independer . of chemotherapy duration. A similar correlation between chemotherapy dose and risk of ANL was suggested but could be proven with the available data. An apparent association between ANL risk and indolent NHL histological subtypes was due to the significantly larger amounts of potentially leukemogenic therapy to which these patients were repeatedly exposed. Only one case of ANL occurred among NHL patients whose nitial therapy produced a durable complete remission. Our data are compatible with a multistep model of leukemogenesis and also underscore the need for curative NHL treatment regimens which minimize the duration and quantity of therapy required for optimum patient management.

INTRODUCTION

With the advent of improved survival in many patients with advanced cancer and the increasing use of adjuvant therapy in cancer patients with minimal tumor burdens. the need for quantitative data on late complications of such therapy has increased. Of special concern is treatment-induced leukemia. a phenomenon most prominent following the use of alkylating agents in patients with ovarian cancer (42. 46). multiple myeloma (4). and polycythemia vera (5) and following combined radiation and chemotherapy in patients with Hodgkin's disease (30. 54. 56). The Environmental Epidemiology Branch. National Cancer Institute. in collaboration with the Division of Cancer Treatment, has undertaken a series of studies systematically designed to clarify quantify the carcinogenic risk of specific treatment modalities, both to optimize risk-benefit decisions in patient care and to elucidate mechanisms of cancer induction in humans (7). The assessment of ANL[3] in patients treated for NHL, reported here is part of this program.

METHODS

Cohort Study. We evaluated the occurrence of second cancers among 517 patients with NHL who were treated on various National Cancer Institute protocols between 1954 and 1975. Patients who had not been seen at the Clinical Center within 3 months of the study closing date were actively followed up; 510 (99%) were successfully located. and their second tumor status was determined. The cohort analysis was based on a computer file created for clinical studies on these patients; the file included basic demographic data and general information on disease and treatment. Initial therapy was characterized by type of radiation (involved or extended field. TNR. TBI. or HBI) and chemotherapy (single agent. combined agents). Details of radiation dose. specific drug type and dose. and subsequent therapy were not part of this computer file. All NHL biopsy material was reviewed and classified according to the Rappaport nomenclature (20). Objective documentation of all second cancers was obtained, and all leukemia cases were histologically reviewed and confirmed by Dr. Harvey Gralnick. Chief, NIH Clinical Center Hematology Service. Leukemic transformations of NHL, which occurred in approximately 14% of these patients (12), were not considered second primaries

Expected incident cancers for all sites combined (excluding nonmelanoma skin cancer) and for specific sites were estimated by applying sex-, 5-year age-, and 5-year calendar time-specific incidence rates from the Connecticut Tumor Registry (14) to the corresponding person-years at risk. The study cohort was 93% Caucasian and thus similar to the racial profile of the Connecticut Tumor Registry. Specially prepared tabulations for acute myelogenous leukemia. acute monocytic leukemia. other (nonlymphocytic) acute leukemia, and acute leukemia not otherwise specified were combined to produce ANL rates for males and females.' Person-years were accumulated from the date of NHL diagnosis to the date of second primary cancer. date of death, or closing date of study (January 1980), whichever came first. using the computer program of Monson (39).

Our measure of RR was the ratio of observed to expected cases. Excess risk $\left(\frac{\text{observed cases} - \text{expected cases}}{\text{person-years of observation}}\right)$ was also computed, with statistical significance determined by assuming that the observed number of cases was distributed as a Poisson variable (48). Exact 95% CL were computed by Fisher's method. If the lower limit was > 1.0, the ratio of observed to expected cases was considered significantly ele-

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[3] The abbreviations used are: ANL. acute nonlymphocytic leukemia: NHL. non-Hodgkin s lymphoma. RR, relative risk; CL. confidence limits: NPOL. nodular poorly differentiated lymphocytic lymphoma: NML. nodular mixed lymphoma: DWDL. diffuse Hell-differentiated lymphocytic lymphoma, TNR, total nodal radiation; TBI. total-body radiation. HBI. hemibody radiation.

[4] J. T Flannery (Director. Connecticut Tumor Registry), personal communication.

vated ($p < 0.05$). Cumulative ANL risks were computed using the Kaplan-Meier life table technique (53).

Case-Control Analysis. Since details of treatment and information on ANL risk factors were not available from the main computer file, a case-Control study within the NHL cohort was undertaken. NHL patients who developed second cancers of interest (*i.e.*, ANL. lung cancer) were each matched to 4 NHL patients without second cancer. Selection criteria included sex. race, age (±5 years). and duration of survival. The record of each patient was then abstracted in detail for type, port and dose of radiation: total dose of each specific anticancer drug: duration of treatment (months. cycles); pre-NHL radiation exposure: tonsillectomy: infectious mononucleosis and autoimmune disease: family history of cancer: occupation: exposure to toxic chemicals: and smoking status.

Cumulative Sone marrow radiation dose. averaged over the entire body. was estimated for each patient by multiplying the proportion of total-body active bone marrow encompassed by each treatment port (18) times the radiation dose delivered to that port and summing for all radiation treatments. Patients were classified as having no marrow radiation exposure (cumulative dose. 0 rads). "medium" exposure (6700 rads). or high exposure (>700 rads). We acknowledge that this method is. at best. a crude approach to the difficult task of estimating total bone marrow radiation dose. an approach that cannot take into account differences between the various radiation therapy modalities or important issues such as treatment volume. fractionation, or dose rate. We chose the analytic technique of Court Brown and Doll (15), as this method represents the only reasonable dose-estimation technique currently available. but our results must be evaluated with its limitations in mind. The vast majority (95%) of patients studied in detail received MV radiation. In the absence of a comparable method for determining cumulative chemotherapy dose in patients who received multiple agents. duration of chemotherapy was chosen as the index of drug exposure. Three levels of chemotherapy exposure were delineated by stratifying cases and controls combined into 3 groups of equal size low (≤3 months of Chemotherapy): medium (4 to 8 months): and high (28 months). On this basis. each patient was' then classified into one of 9 possible radiation-chemotherapy exposure categories. RRs and trends in this portion of the analysis were assessed using the Mantel extension test (48).

Correlation coefficients obtained in matched pairs analysis indicated that matching was not necessary to control confounding (48); therefore, an unmatched analysis was conducted. Standardized relative risks and Mantel-Haenszel summary point estimates (RR) were computed: interval estimation for these ratios was calculated using the test-based procedure of Miettinen (48).

RESULTS

Cohort Analysis

General. There were 312 males and 205 females in the study cohort. The mean age at NHL diagnosis was 43.4 years. Overall, 2203 person years of observation were accrued, with an average follow-up of 4.3 years (range, 0 to 22 years) Twenty-one cases of second cancer were diagnosed (Table 1), compared to 11 4 expected (ratio of observed to expected cases. 1 8, 95% CL 1 1;2.8) This excess was due entirely to ANL with 9 cases observed, compared to 0 08 cases expected (ratio of observed to expected cases, 105; 95% CL, 48;199). The ANL risk in males was twice that in females The excess risk of ANL increased with advancing age at first NHL treatment, although not significantly <30 years = 2 9 cases/1000/year; 35 to 49 years = 3 6 cases/1000/year; 50+ years = 5.7 cases/1000/year The first case of ANL occurred 18 months after NHL diagnosis. and the last occurred at 10 years (Table 2). Within the constraints imposed by small numbers at longer periods of follow-up, no decrease in ANL risk has yet been observed, although no ANL cases been observed after 10 years (Chart 1)

All 9 patients with ANL were classified as having acute myelogenous leukemia (Table 3). The mean latent period between the diagnoses of NHL and ANL was 68 months An antecedent preleukemic phase charactenzed by pancytopenia and dysmyelopoietic bone marrow morphology was typical Eight of 9 patients had indolent NHL subtypes 6 NPDL, one NML and one DWDL By comparison, 44% of the entire cohort had one of these 3 subtypes (20, 16, and 8%, respectively) These patients typically received multiple courses of therapy and survived only briefly following the development of ANL Two additional patients died following septic complications of severe myeloproliferative disorders (Table 3), both thought to represent preleukemic states (19, 34. 41, 43) Cytogenetic studies on most of these patients have been reported previously (59).

No statistically significant excess of other cancer was noted although 4 cases of bronchogenic carcinoma were excluded from the formal cohort analysis because they were diagnosed incidentally at autopsy (Table 4). Careful pathology review

Table 2
Observed and expected cases of ANL by interval after NHL diagnosis

interval (yr)	n	ANL Observed	ANL Expected
<1	517	0	0 01
1–2	372	2	0.02
3–5	272	4	0.03
6–9	146	2	0.02
10+	40	1	0.01

[a] Rounded off to 2 places to the right of the decimal
[b] O/E ratio of observed to expected cases

Table 1
Sex specific observed and expected cases of second cancer by cancer site

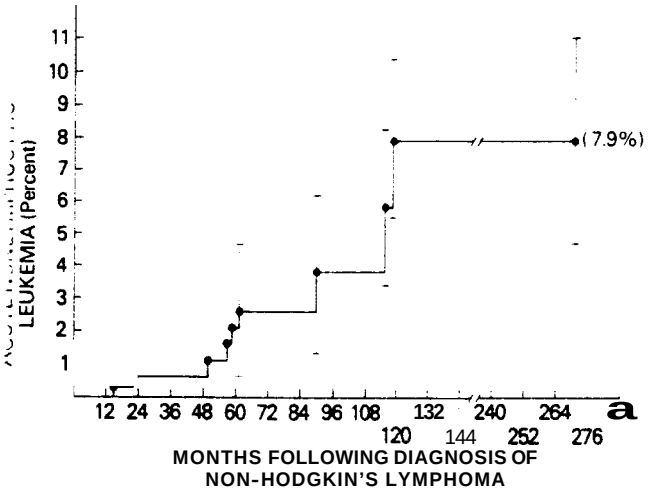
Cancer site	M Observed	M Expected	M O/E[a]	F Observed	F Expected	F O/E	Total Observed	Total Expected
All sites[b]	14	6 4	2 2[c]	7	5 0	1 4	21	11.4
ANL	7	0 05	1300[c]	2	0 03	630[c]	9	0.08
Colon rectum	2	1.0	1 9	1	0 7	1 4	3	1 7
Prostate	3	0 7	4 4				3	0.7
Lung[d]	0	1 3		2	0 3	7 4	2	1.6
Buccal cavity	1	0 4	2 6	0	0 1		1	0.5
Pancreas	0	0 2		1	0 1	a 0	1	0.3
Cervix				1	0 5	2 1	1	0.5

[a] O/E ratio of observed to expected cases
[b] includes one patient with disseminated carcinoma of unknown primary site
[c] $P < 0.05$
[d] Four cases diagnosed only at autopsy are excluded frorr this analysis

d that all 4 cases would have become clinically manifest had nts survived longer. If these cases had been diagnosed ;m, a statistically significant lung cancer excess would e resulted. Four of these 6 cases had extremely short latent ods (2,8, 9, and 14 months), making it very unlikely that therapy played a primary role in their pathogenesis. Case fact, had a "pulmonary scar" on chest X-ray at the time of diagnosis. At autopsy 18 months later, this sheet metal ker, a heavy smoker, had an area of dense fibrosis and ring in which his lung cancer developed. The casecontrol y indicated that NHL patients who developed lung cancer ? significantly more likely to have been cigarette smokers than were NHL controls (RR. 15.0; $p < 0.05$), although this risk estimate is deceptively high because the NHL controls were less likely to smoke cigarettes (only 28% ever smoked) than the population at large.

Two of the 3 prostate cancers were diagnosed during the first year after NHL diagnosis. They probably represented occult cancers. with ascertainment enhanced among patients under careful clinical observation.

Leukemia Risk by Initial Therapy. The leukemia risk seemed greatest among intensively irradiated patients, *i.e.*, those initially treated with TNR, TBI, or HBI. All 7 of the "radiation-related" ANL cases occurred among the 99 NHL patients who initially received one or more of these treatment modalities. Unfortunately. these data give an inaccurate picture of the treatment association with ANL risk, since the clinical data file did not reflect patients' complete treatment experience. Chart 2 and Table 2 illustrate that 7 of the 9 ANL cases occurred in patients



hart 1 Mean cumulative (life table) risk of 4NL among patients with NHL by :al following NHL diagnosis *Bars* S E

Table 4

NHL patients *with* lung cancer: clinical summary

			NHL	Lung cancer			
Case	Age	Sex	His-tol-ogy	Latent period (mos.)	Cell type	Survi-val (mos.)	Smoking status
1	39	F	NML	2	Aaenocarcinoma	2	77 pack-yr
2	45	F	DWDL	52	Adenocarcinoma	20	10 pack-yr
3	63	M	DPDL[a]	9	Epidermoid	[b]	40 pack-yr
4	68	M	NPDL	8	Adenocarcinoma	[b]	50 pack-yr
5	69	M	NPDL	68	Bronchiolar	[b]	Non-smoker
6	68	F	DML	14	Epidermoid	[b]	Unknown

[a] DPDL diffuse poorly differentiated lymphocytic lymphoma, DML. diffuse mixed lymphoma

[b] Diagnosec at autopsy

Table 3

NHL patients with ANL and *myeloproliferative disorders. clinical* summary

			NHL	Leukemia					
Case	Age	Sex	Histology	Preleukemia	Latent period (mos.)	Type	Survival (mos)	First NHL treat-ment	Subsequent NHL treatment
1	33	M	DPDL[a]	No	18	AML	1	CV (6 cycles)	PrV (2cycles) cervical node RT (2531R)
2[b]	28	M	NPDL	Yes	91	AML	3	TBI ,200 R) TNR (2000R)	TBI (50 R) C (17 mos) UHBI (500 R); pelvic RT (150 R) C (6 mos) CVP (4 cycles) liver RT (300 R)
3"	48	M	DWDL	Yes	59	AML	9	UHBI (500 R) LHBI (500 R)	TBI (310 R)
4	47	M	NPDL	Yes	120	AML	10	TNR (3000 R)	
5"	57	M	NPDL	Yes	32	AML	10	UHBI (600 R); LHBI (600 R)	TBI (130 R). TBI (100 R). CVP (5 cycles). Bu (2 mos); knee RT (200 R)
6[b]	63	M	NPDL	Yes	58	AML	1	TBI 1250R); TNR (2000R)	Spleen RT (700 R); TBI (40 R)
7"	62	M	NML	Yes	61	AML	1	TNR (2160 R)	UHBI (250 R). LHBI (250 R). TBI (25 R). lung RT (450 R); CVP (6 cycles)
8	48	F	NPDL	No	115	AML	1	MOPPr (6 cycles)	C (7 yr) gastric RT (2520 R). BACOP (6 cycles)
9"	65	F	NPDL	Yes	58	AML	4	UHBI (500 R); LHBI (500 R)	Cervical node RT (600R); TBI (40 R). CVP (29 cycles)
lopro-ative rders									
10	30	M	DWDL		118	MMS	38	UHBI (500 R); LHBI (500 R); TNR (2000 R)	CVP (8 cycles); VB (2 mos.): S; Ch: TBI (100 R); liver RT (300 R)
11[b]	24	M	NPDL		71	MMS	10	TNR (3500 R)	UHBI (500 R). LHBI (500 R); epitrochlear RT (500 R); TBI (120 R)

DF iffuse poorly differentiated lymphocytic lymphoma: AML. acute myelogenous leukemia; C. cyclophosphamide; V. vincristine: Pr. procarbazine: RT. radiation apy: UHBI. upper hemibody radiation; P. prednisone: LHBI, lower hemibody radiation; Bu. busulfan; M. nitrogen mustard; O. Oncovin. B. bleomycin; A. Adriamycin; S. malignant myeloproliferativesyndrome; S. streptozotocin; Ch. chlorambucil.

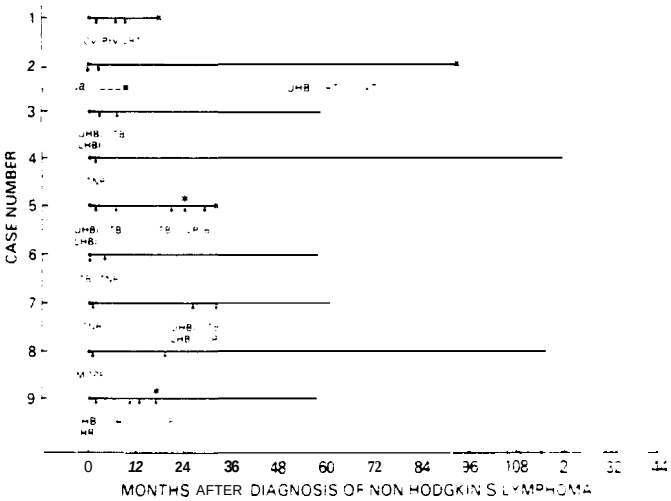


Chart 2 Schematic outline of treatments received by NHL patients who developed ANL *See* Table 3 for details of drug and radiation doses ● diagnosis of NHL × diagnosis of ANL . point at which initially radiated patients received their first chemotherapy *LHBI* lower hemibody radiation *UHBI* upper hemibody radiation *LRT* local radiation therapy *C* cyclopnospharnide V vincristine P prednisone *Pr* procarbazine M nitrogen mustard *B* bleomycin *Bu* busulfan *A* Adriamycin O Oncovin

receiving multiple courses of both radiation and chemotherapy. The case-control study thus provided better quantitative data on treatment associations (see below). The excess risk of ANL in the entire cohort was 4.1 cases per 1000 patients per year. The cumulative (life table) risk of ANL at 10 years was 7.9% overall.

Leukemia Risk by NHL Characteristics. NHL patients who presented with nodal disease in advanced stages but without "B" symptoms appeared most likely to develop ANL (Table 5). More detailed analysis revealed that these characteristics were indirect indices of the association between ANL risk and NHL histological subtype: 8 of 9 ANL patients had "indolent" histological subtypes (*i.e.*, NPDL, NML. DWDL) with 6 having NPDL.

Case-Control Analysis

When NHL patients who developed ANL were compared to age-, sex-, race-, and duration of survival-matched NHL patients who did not develop second cancers, the association between leukemia risk and NHL subtype persisted. NPDL was found in 6 cases (67%) and only 6 controls (17%) (RR, 10.0; $p < 0.05$), with a similar pattern observed when all indolent histological subtypes were considered. Thus, the relatively long survival experienced by these subgroups of NHL patients cannot, per se, account for their high risk of ANL.

Similarly, the association between initial radiation treatment and risk of ANL also persisted for TNR (44 versus 3%; RR. 28.0) and TBI (67 versus 22%; RR. 7.0). both significant differences. No statistically significant associations were observed between specific chemotherapeutic agents or combinations of drugs and ANL risk. The strongest association observed was for cyclophosphamide (67 versus 58%; RR, 1.4).

Since the case-control study included data on all treatment received by study patients, these individuals could be classified as ever having been exposed to chemotherapy alone, radiatioh alone. or both (Table 6). Six cases (67%) compared to 8 controls (22%) received both radiation and chemotherapy; this distribution is significantly different from what might be expected by chance ($p < 0.02$). Two of the remaining cases received multiple courses of radiation therapy which included TBI. When ANL risk arnorg NHL patients who received both radiation and chemotheraoy was compared to that of NHL patients treated with only one modality, a significant difference was observed (RR, 6.0: $p < 0.05$). This increased ANL risk among combined-modality patients persisted when adjusted for histological subtype. suggesting that confounding by this variable cannot account for the association observed. Similarly, the ANL risk among patients with indolent histological subtypes persisted when adjusted for combined- versus single-modality therapy, indicating that exposure per se to combined-modality treatment cannot account for this association.

Patients who developed ANL were more intensively treated than were controls. For example, all cases were exposed to some radiation, compared to 22 (61%) controls. Furthermore. the mean number of radiation therapy courses was 3.1 for cases and 1.5 for controls. The average radiation dose to the active bone marrow was significantly greater for cases (1180 rads) compared to controls (490 rads) ($p < 0.05$). With regard to chemotherapy dose, exposed cases received an average of 3 times more cyclophosphamide than did exposed controls (71,700 mg versus 23,300; $p < 0.01$). Similarly, mean duration of cyclophosphamide therapy was significantly longer in cases (28.5 months) than in controls (10.5 months). No other significant differences in drug doses were observed.

To further assess dose-response relationships and drug-radia-

Table 5
Observed and expected cases of *ANL* by various *NHL variables*

Variable	n	Leukemia		O/E[a]
		Observed	Expected	
Site				
Nodal	370	a	0 07	
Extranodai	87	1	0.01	
Stage				
I-II	111	1	0.02	
III-IV	398	a	0.06	
Symptoms				
Absent	319	a	0.06	
Present	190	1	0.02	
Architecture				
Nodular	249	8	0.06	
Diffuse	233	1	0.02	
Mixed	35	0	0.004	
Cell type				
Lymphocytic	214	a	0.05	
Histiocytic	147	0	0.02	
Mixed	117	1	0.02	
NPDL	105	6	0.02	

[a] O/E. ratio of observed to expected cases

Table 6
NHL and *ANL* case-control study ever exposed to *specific treatment*

Treatment	Cases	Controls
Chemotherapy only	0	
Radiation only	3	
Both	6	
Tota!	9	

[a] One control was treated with surge? only.

Table 7

assification of NHL and ANL cases and controls by level of exposure to radiation and chemorherapy

	Chemotherapy[b]							
	Low		Medium		High		Total	
	Case	Con-troi	Case	Con-troi	Case	Con-troi	Case	Con-troi
	0	2	0	7	0	5	0	14
n	0	0	1	4	2	3	3	15
	3	2	2	3	1	2	6	7
	3	12	3	14	3	10	9	36

N 3 rads medium ≤700 rads, high >700 rads
N ≤3 months of treatment medium 4 to 8 months high >8 months

nteractions in ANL risk, each patient was classified into one radiation-chemotherapy exposure levels (see Table 7). as ibed in "Methods." Inspection of the marginal totals in e 7 reveals roughly equal proportions of cases and controls sh of the 3 chemotherapy exposure categories, in contrast creasing numbers of cases and decreasing numbers of ols as one progresses from low- to high-radiation exposure os. The RR of ANL in the high-radiation exposure group pared to the 2 lower exposure groups combined is 8.1 (9596 .8;36). Controlling for duration of chemotherapy, there was nificant trend of increasing ANL risk with increasing cumue bone marrow radiation dose ($\chi_{M-Ext} = 2.965 p < 0.05$). contrast to the data on cyclophosphamide dose cited above. ssociation between duration of chemotherapy and ANL risk observed in this analysis. Duration of chemotherapy may cc irately reflect the total cytotoxic drug exposure of pang patients treated for >8 months, the mean duration enotherapy was 52 months for ANL cases, compared to onths for controls. Further stratification of chemotherapy ion was not practical given the small numbers of patients ANL. If one considers cyclophosphamide, the most fre-ly used cytotoxic agent in these patients, the mean dose g) received by ANL cases in the "medium" and "high" on of chemotherapy categories was 18.500 and 124,900. ctively. In contrast. the mean cyclophosphamide dose re-d by controls was 8.200 and 40,200 in the same 2 cate-s. Finally, 3 cases (33%) received over 2 years of chemo-py, compared to only 3 controls (8%). These observations est that using duration of treatment as an index of chemo-py exposure may mask important dose trends which might vident were there a reasonable method for aggregating s of different drugs into a single dose parameter for each nt.

ally, based upon the data collected from the char! review, llowing factors did not contribute to the ANL nsk in this : family history of cancer: occupation; exposure to toxic icals; pre-NHL radiation exposure; autoimmune disease; ious mononucleosis; or tonsillectomy. Case 3 did have sive occupational exposure to pesticides, herbicides, and icals.

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his cohort of NHL patients. the risk of ANL was 105 times ex ed from general population rates, with a cumulative ar nsk of ANL equal to 7 9% Two additional patients died ing septic complications of severe myeloproliferative disorders (Table 3). Had they lived longer, current evidence Suggests that evolution into frank ANL might have occurred (19,34. 41, 43). The risk of ANL increased by a factor of 2 to 3 in NHL patients with indolent histological subtypes who were treated with multiple courses of combined-modality therapy. These associations persisted in the more detailed case-control analysis, suggesting that neither long survival nor confounding by histology accounted for the associations observed. The critical determinant of ANL risk in this context was the amount of treatment received, especially if both radiation and chemotherapy were used. Our data document that NHL patients who developed ANL received considerably more therapy, both radiation and drugs, than did comparable NHL patients who did not develop ANL. We have demonstrated that the risk of ANL increases as the estimated cumulative radiation dose to the bone marrow increases, the first such evidence of a radiation dose-response relationship in cancer treatment-related ANL. Our finding requires further evaluation in view of the methodological problems cited above and the limited number of patients available for study. This analytical method has been used in several previous studies (8.15) and was reviewed recently by the Committee on the Biological Effects of Ionizing Radiation (13). They concluded that while reasonable. "the estimates of radiation doses absorbed . . . are imprecise and must be further corrected as new information becomes available," a view with which we concur. However. the very broad radiation dose categories used make it improbable that more refined dose estimation techniques would result in significant changes in dose category of patients. Furthermore, it is of particular interest that the risk of radiogenic leukemia estimated from our data, 3 cases per million patients exposed per year per rad, is consistent with current estimates from lower-dose studies (13). The etiological importance of radiation in this series of ANL is underscored by the observation that 3 of the 9 cases were treated with high-dose radiation only, receiving TNR. HBI, and/or TBI in multiple courses.

Our data also suggest a correlation between chemotherapy dose and risk of ANL. although the lack of a cumulative chemotherapy dose measure and the limited number of ANL cases have thus far prevented a definitive answer to this question. Duration of chemotherapy did not seem to be a satisfactory index of drug exposure, at least within the constraints imposed by the small number of ANL patients available for study. Support for a chemotherapy dose-response effect is found in the observations that. compared to controls, cases *(a)* had a significantly higher mean cyclophosphamide dose overall and within each of the 3 chemotherapy duration strata: *(b)* had a significantly longer duration of cyclophosphamide treatment, both overall and within the high chemotherapy duration stratum; and (c) were more likely to have received chemotherapy for greater than 2 years.

The fact that 8 of the 9 ANL cases (and both patients with myeloproliferative syndromes) were repeatedly exposed to potentially leukemogenic treatment (Chart 2) is probably not a coincidence. The remitting-relapsing course experienced by patients with indolent NHL subtypes led to repeated therapeutic intervention over a period of many years, resulting in disproportionate exposure of these patients to potentially leukemogenic agents. Such a pattern is compatible with a "multihit" model of leukemogenesis (29) and resembles the risk of ANL following combined-modality treatment of Hodgkin's disease (30,54, 56). It differs from ANL following ovarian cancer (42,46), multiple myeloma (4), and polycythemia vera (5), where alkylating agents

alone seem responsible for the ANL risk. In these latter diseases, small-port radiation therapy is used. and TNR, TBI, and HBI are seldom used. Conceptually. protracted TBI and HBI may be analogous to the chronic administration of "radiomimetic" alkylating agents.

The very high relative. excess. and cumulative risks of ANL in our cohort may be due, in part, to the extensive use of TBI and HBI, treatment modalities which expose large volumes of bone marrow to relatively low cumulative doses of radiation. These approaches were used under research protocols now completed and no longer in use at this institution. The leukemogenic potential of such exposures has been well documented in both laboratory (55) and human (13) studies. It is noteworthy that high-dose radiation therapy alone to smaller treatment volumes generally has not been leukemogenic in humans (6). Laboratory experiments have indicated that high doses of radiation cause cell death. while lower doses may cause nonlethal cellular injury which may enhance malignant transformation (38).

The literature on the occurrence of ANL in patients with NHL is largely anecdotal. although Zarrabi et al. (61, 62) have published 2 estimates of ANL risk in this setting. suggesting RRs of 10 and 37. respectively. More recently. Harousseau et al. (24) reported that the actuarial risk of ANL was 4.5% at 5 years in their series of patients, an estimate similar to our own. In contrast. a Canadian study of 630 patients with NHL found no cases of ANL (37). These latter NHL patients received combined-modality therapy less often than did our patients.

The case reports of this association are numerous and becoming more so (3, 9. 10, 17. 19. 21. 24–28. 31, 32. 34–37. 40. 57. 58. 60–62); our literature review identified 104 cases. In the aggregate, these reports reveal a male excess (68 males. 30 females, 6 unspecified), a mean age at NHL diagnosis of 48 years (range. 5 to 83). and an average latent period of 5 years. Fifty-six patients (54%) received both radiation and chemotherapy, while 28 received chemotherapy alone and 12 had radiation alone. The ANL subtype most frequently reported was acute myelogenous leukemia (64 cases). followed by acute myelomonocytic leukemia (17 cases), acute erythroleukemia (9 cases). and acute monocytic leukemia (3 cases). NPDL was the most frequent histological subtype (38 cases), even though many of these reports antedated the Rappaport nomenclature: 53 patients had an indolent histological subtype.

These clinical observations suggest that ANL risk for males with NHL might be greater than that for females. In fact. our data show that males are at twice the risk of ANL than are females. a difference which is not statistically significant partly because of the small numbers involved. We were unable to examine this association in the case-control study because sex was a matching variable. Males have higher leukemia rates than do females in the general population (1) and also following radiation exposure (13). Since sex-specific incidence rates were used to generate expected numbers of ANL in our study, this male leukemia predisposition cannot account for our observation. Furthermore. indolent histological subtypes were equally frequent in males (43%) and females (45%). It seems possible that the leukemogenic exposures to which NHL patients are subjected exacerbate the intrinsically higher leukemia risk in males, but the mechanism for such an effect remains obscure. Although, the age effect we observed was not statistically significant. the trend is consistent with observations made in adult Japanese survivors of the atomic bomb (13) and with recent data obtained from patients with ankylosing spondylitis (50) and Hodgkin's disease (11). all of which suggest a positive correlation between age at exposure and risk of ANL.

In understanding the relationship between NHL treatment and ANL risk. it is important to know whether there is an increased risk of ANL in NHL patients who have not received potentially leukemogenic therapy. since it has been suggested that patients with certain lymphoproliferative cancers, multiple myeloma for example (47), may be at risk of developing ANL independently of therapy. No cases of ANL have been reported among 4223 patients with lymphoma and myeloma in the Connecticut Tumor Registry followed up during the prechemotherapy era (49), although the survival of these patients may have been too brief to permit the development of ANL. However, of the 104 cases reported to date. 6 represent instances in which the NHL and ANL were diagnosed simultaneously (27. 28. 31, 35. 36. 60) while in 9 cases. the ANL developed less than 1 year after NHL diagnosis (25. 27, 28. 51. 62). Therapy clearly played no role in the first group. and its role in the second group seems doubtful in view of the very short latent period. These observations suggest that patients with NHL are intrinsically prone to ANL although an additional leukemogenic role for therapy seems inescapable, especially given the dose-response relationships we have described. Combined-modality therapy may act by exacerbating the intrinsic association between NHL and ANL whatever it might be. The presence of a leukemic predisposition in NHL patients may also explain, in part. the very large RR observed in such patients following treatment.

With regard to lung cancer, it is noteworthy that several case series (2. 22, 44) and 2 analytical studies (23.33) have suggested that patients with lymphoproliferative cancers are prone to bronchogenic carcinoma. One study documented that the association observed was independent of therapy (23), a finding supported by our data as well. The case-control study indicated that NHL patients who developed lung cancer were significantly more likely to be smokers than were controls, but the magnitude of this risk did not suggest an interaction between smoking and other lung cancer risk factors. Whatever the mechanism of this association, the presence of or development of an isolated pulmonary lesion in patients with NHL must be approached with the possibility of primary lung cancer in mind.

What implications do these findings have for the management of patients with NHL? *(a)* Although the relative and cumulative ANL risks in this cohort are striking, this should not obscure the fact that, in absolute terms, this complication is infrequent, i.e. 4.1 ANL cases per 1000 patients per year. *(b)* The value of aggressive therapy for some NHL patients has been well demonstrated by the cure rates for diffuse histiocytic lymphoma which now approach 50% for a disease until recently considered incurable in most patients (16. 52). Patients with agressive NHL histologies, for the most part, are either cured by their initial therapy or rapidly succumb to their disease. In either case they do not receive repeated or prolonged therapy. Our data revealed only one case of ANL among NHL patients whose initial therapy produced a durable complete remission requiring no additional treatment. In contrast, patients with "indolent" NHL subtypes are not readily cured by existing treatments (45) and are thus repeatedly exposed to potentially leukemogenic therapy over a period of years in an effort to control their disease. Eight of the

ANL cases in our study occurred in this subgroup. suggesting
at this approach produces Serious late effects with questiona-
vival benefit This underscores the importance of a contin-
earch for curative NHL treatment regimens. which will
imize the duration and quantity of therapy required for optimal
tient care

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DDENDUM

ollowing acceptance of this manuscript an additional report suggesting that e is an etiological association between malignant lymphoma and lung cancer appeared (Konits P H Aisner J Whitacre M and Wiernik P Lung cancer complication of prolonged survival in patients with lymphoma Med Ped ol *10* **331-338 1982)** In addition a new series of treatment-related ANL in ents with YHL has been published which confirms our observation that risk is test in patients receiving TBI plus chemotherapy{Gomez G A Aggarwal K and Han T Posttherapeutic acute malignant myeloproliferative syndrome and e nonlymphocytic leukemia in non-Hodgkin s lymphoma Cancer (Phila) 50 5-2288 1982]

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