ACUTE NONLYMPHOCYTIC LEUKEMIA AFTER THERAPY WITH ALKYLATING AGENTS FOR OVARIAN CANCER

A Study of Five Randomized Clinical Trials

MARK H. GREENE, M. D., JOHN D. BOICE, JR., SC. D., BENJAMIN E. GREER, M. D., JOHN A. BLESSING, PH. D., AND ALON J. DEMBO, M.B.

Abstract We evaluated the occurrence of acute nonlymphocytic leukemia (ANL) among 1399 women with ovarian cancer who were treated in five randomized clinical trials. Of the 1399 women, 998 had been treated with alkylating agents, and among these, 12 cases of ANL were observed; the expected number was 0.11. Ten patients with ANL had received melphalan, and two chlorambucil. ANL was not observed in 401 women who had been treated with surgery or radiation or both, without alkylating agents. The excess risk of ANL that was associated with alkylating-agent therapy was 5.8 cases per 1000 women per year, and the cumulative seven-year risk of ANL was 9.6±3.3 per cent (±S.E.). The risk of ANL among patients who were treated with chemotherapy alone was indistinguishable from that observed in patients receiving both radiation and chemotherapy. A positive correlation between initial drug dose and the risk of ANL was suggested. These data underscore the need to assess other cytotoxic agents and regimens of drug administration to identify those that do not have harmful late effects. (N Engl J Med. 1982; 307:1416-21.)

EXPERIMENTAL data have long indicated that some anti-cancer drugs, particularly the alkylating agents, are carcinogenic in laboratory animals.[1] Until recently, evidence that these agents have similar effects in human beings has been anecdotal. During the past five years, however, a series of analytic studies have documented excesses of acute nonlymphocytic leukemia (ANL) in patients treated for Hodgkin's disease,[2-4] multiple myeloma,[5,6] non-Hodgkin's lymphoma,[7,8] polycythemia vera,[9] and ovarian cancer.[10,11] Studies of women with ovarian cancer have been particularly informative, since an intrinsic predisposition to ANL has been clearly ruled out.[10] Furthermore, the leukemogenic effects of radiation alone, alkylating agents alone, and both treatments combined can be assessed, since each has its place in the management of this disease. Finally, ovarian cancer occurs relatively frequently, and even patients with an advanced malignant condition may survive long enough to be at risk of delayed complications of therapy.

From the Epidemiology Branch, National Cancer Institute, Bethesda, Md.; the Department of Gynecology, M. D. Anderson Hospital, University of Texas System Cancer Center, Houston; the Gynecologic Oncology Group, Buffalo; and the Department of Radiation Oncology, Princess Margaret Hospital, Toronto, Ont,, Canada. Address reprint requests to Dr. Greene at the Environmental Epidemiollogy Branch, National Cancer Institute, Landow 4C-18, Bethesda, MD 20205.

Research to date has focused on demonstrating the risk of ANL, but a number of important questions remain: Which specific chemotherapeutic agents are associated with the risk of ANL? Is there a dose-response relation between drug exposure and the risk of ANL? Do drugs and ionizing radiation act together to increase the risk of ANL beyond that associated with each treatment method alone?

The Environmental Epidemiology Branch of the National Cancer Institute, in collaboration with the Division of Cancer Treatment, has undertaken a series of studies designed to clarify the magnitude and determinants of the risk of a second cancer after anti-cancer therapy.[8,10,12-16] This report on the risk of ANL among patients with ovarian cancer is part of that program. Our data indicate that exposure to the alkylating agents melphalan and chlorambucil was responsible for the development of ANL in the five trials we studied.

METHODS

Clinical Trials

We evaluated the occurrence of ANL among 1399 patients with ovarian cancer who were treated in five randomized clinical trials (Table 1), conducted by investigators at the M. D. Anderson Hospital,[17] the Gynecologic Oncology Group,[18-20] and the Princess Margaret Hospital.[21] Basic demographic information and data on the

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Table 1. Participating Clinical Trials and Treatment Regimens.

Trial	Stage of Disease	No. of Patients	(Arm) Treatment Regimens *
M.D. Anderson Hospital (ref. 17)	I, II, III, IV †	89	(1) Pelvic/abdominal irradiation
		83	(2) M: 1 mg/kg every 4 weeks × 12 cycles
Gynecologic Oncology Group Trial 1 (ref. 18)	I	68	(1) Observation after surgery
		55	(2) Pelvic irradiation
		72	(3) M: 1 mg/kg every 4 weeks × 18 cycles
Gynecologic Oncology Group Trial 2 (ref. 19)	III, IV	96	(1) Pelvic/abdominal irradiation
		87	(2) M: 1 mg/kg every 4 weeks × 3 cycles
		85	(3) M (same regimen) followed by irradiation
		78	(4) Irradiation followed by M (same regimen)
Gynecologic Oncology Group Trial 3 (ref. 20)	III, IV	137	(1) M: 1 mg/kg every 4 weeks until progression
		113	(2) M + 5FU (15 mg/kg/day × 5) every 4 weeks until progression
		118	(3) M + 5FU (8 mg/kg/day × 5) + Act-D (0.5 mg/day × 5) every 4 weeks until progression
		73	(4) C (7 mg/kg/day × 5) + 5FU and Act-D (as in arm 3) every 4 weeks until progression
Princess Margaret Hospital (ref. 21)	I, II, III ‡	28	(1) Observation after surgery
		146	(2) Pelvic irradiation ±AMS
		71	(3) Pelvic irradiation + Ch: 6 mg by mouth every day for 2 years

*M denotes melphalan, 5FU 5-fluorouracil, Act-D actinomycin-D, C cyclophosphamide, Ch chlorambucil, and AMS abdominal moving strip radiation.

†Residual tumor after surgery <2 cm; no ascites; no tumor in areas requiring limitation of radiation dose; Stage I was represented by 56 patients, Stage II by 67, Stage III by 45, and Stage IV by 4.

‡Stage I was represented by 71 patients, Stage II by 123, and Stage III (asymptomatic) by 51.

occurrence of ovarian cancer, the occurrence of subsequent cancer, and treatment were collected. The available information on treatment included whether initial and subsequent radiation therapy had been given, whether initial and subsequent chemotherapy had been administered, the names of specific chemotherapeutic agents received, and treatment dates. The dose of every chemotherapeutic agent administered to each patient was not recorded. However, the duration and dose of drug administered during each patient's *initial* course of treatment was determined for participants in the three single-agent trials at the M. D. Anderson Hospital, Princess Margaret Hospital, and Gynecologic Oncology Group Trial 1. To assess the relation between initial chemotherapy dose and risk of ANL, participants in these trials were divided into groups with no drug exposure, "low" exposure, or "high" exposure. "High exposure" was defined as exposure to more than 700 mg for melphalan and more than 2000 mg for chlorambucil. All histologic material was reviewed by Dr. William Velasquez of the M. D. Anderson Hospital Department of Hematology. No additional cytochemistry was performed beyond that employed by the original institution at which each leukemia diagnosis was made. One patient, who was treated with 664 mg of melphalan and who died after septic complications of a preleukemic syndrome, was not counted as an ANL case in the formal analysis.

Analysis

Patients in the five trials were similar with respect to age at diagnosis of ovarian cancer, race, marital status, gravidity, parity, menopausal status, and ovarian-cancer histology. Therefore, all trials were pooled for analysis, with stratification according to the type of therapy received. Analyses were performed according to initial therapy (data not shown) and all therapy for subgroups of patients who had been treated with surgery alone, radiation alone, chemotherapy alone, chemotherapy plus radiation, melphalan (ever), or chlorambucil (ever). To compute expected cases of ANL, specially prepared tabulations from the Connecticut Tumor Registry for specific types of leukemia cells were combined to produce five-year rates of ANL for women that were age-specific and time-specific.[22] Woman-years of observation (WYO) were accumulated from the date of diagnosis of ovarian cancer to the date of onset of ANL, the date of death, or the date of last known status — whichever came first.[23]

Ratios of observed cancers to expected cancers and crude excess risks [(observed cases – expected cases)/WYO] were computed, and statistical significance was determined by assuming the observed number of cases to be distributed as a Poisson variable.[24] Exact 95 per cent confidence limits were computed by Fisher's method. If the lower limit of confidence was more than 1.0, the ratio of observed to expected cancers was considered significantly elevated at the $P<0.05$ level. Cumulative (life-table) risks of ANL were computed using the Kaplan–Meier technique.[25]

Results

Overall, 1399 women with ovarian cancer accrued 3458 woman-years of observation. Patients were followed for a maximum of 11 years (mean, 2.5 years). The mean age at diagnosis of ovarian cancer was 53 years. The women were predominantly white (83 per cent), married (87 per cent), parous (68 per cent), and post-menopausal (85 per cent), with advanced (Stage III/IV, 62 per cent) epithelial cancer of the ovary.

In all five trials, 12 cases of ANL were diagnosed, as compared with 0.18 cases expected (ratio of observed to expected cancers = 67; 95 per cent confidence limits = 34 to 116). The excess risk of ANL was 3.5 cases per 1000 women per year, with a cumulative seven-year risk (±S.E.) of ANL equal to 4.7± 1.6 per cent. The clinical details of these cases, none of which have been previously reported, are summarized in Table 2. The mean age at diagnosis of ovarian cancer was 48 years; five patients had Stage I/II, and seven had Stage III/IV cancer; all were white. The mean latent period between diagnosis of ovarian cancer and diagnosis of ANL was 47 months (range, two to seven years), most had a preleukemic phase, and survival after diagnosis of ANL was brief (median, 4.0 months).

When the cohort was stratified into subgroups according to the type of treatment ever received, all 12 patients with ANL had been exposed to alkylating

Table 2. Characteristics of Patients with Ovarian Cancer Who Acquired Acute Nonlymphocytic Leukemia.

Case No.	Ovarian Cancer								Acute Leukemia			
	Trial *	Age	Stage	Cell Type	Prior Radiation	First Protocol Therapy (Radiation †)	First Protocol Therapy (Chemotherapy ‡)	Subsequent Therapy	Pre-Leukemia	Latent Period	Type §	Survival
										mo		*mo*
1	GOG-1	49	IA	Endometrioid	No	—	M (1190 mg; 21 cycles)	—	No	33	AMMoL	6
2	GOG-3	70	IV	Serous	Yes	—	M (750 mg; 15 cycles)	M (45 mg; 2 cycles	Yes	27	AMMoL	2
3	GOG-3	55	IV	Serous	No	—	M (1530 mg; 26 cycles)	M (60 mg; 2 cycles)	Yes	33	AEL	<1
4	GOG-3	57	III	Serous	No	—	M (1110 mg) + 5FU (66,150 mg) [21 cycles]	C (3528 mg; 9 cycles)	Yes	29	AML	<1
5	GOG-3	48	IV	Serous	Yes	—	M (420 mg) + 5FU (30,000 mg) [12 cycles]	—	Yes	33	AMMoL	1
6	MDAH	27	III	Serous	No	—	M (1062 mg; 19 cycles)	M (587 mg; 10 cycles)	Yes	59	AML	8
7	MDAH	36	III	Mixed	No	AMS (2600 R) + PB (2040 R)	—	M (710 mg; 19 cycles)	Yes	77	AMoL	5
8	MDAH	32	IIB	Serous	No	—	M (960 mg; 12 cycles)	PB; M (2160 mg; 27 cycles) C (6750 mg)	Yes	83	AML	1
9	MDAH	48	IB	Endometrioid	No	—	M (954 mg; 12 cycles)	—	Yes	70	AML	3
10	MDAH	63	IC	Serous	No	—	M (798 mg; 12 cycles)	HAC (12 cycles)	Yes	56	AML	7
11	PMH	56	IIIB	Serous	No	PR (4500 R)	Ch (2977 mg)	—	No	27	AMMoL	18
12	PMH	54	IIC	Endometrioid	No	PR (4500 R)	Ch (2114 mg)	—	Yes	41	AML	10

*GOG denotes Gynecologic Oncology Group Trial, MDAH M.D. Anderson Hospital, PMH Princess Margaret Hospital.

†Radiation therapies: AMS abdominal moving strip, PB pelvic boost, PR pelvic irradiation.

‡Chemotherapies: M melphalan, 5FU 5-fluorouracil, C cyclophosphamide, H hexamethylmelamine, A Adriamycin (doxorubicin), Ch chlorambucil.

§Leukemia types: AMMoL acute myelomonocytic leukemia, AEL acute erythroblastic leukemia, AML acute myelogenous leukemia, and AMoL acute monocytic leukemia.

agents (Table 3). No ANL developed in patients who were treated only with surgery or radiation or both; one patient with ANL had been randomized initially to receive radiation therapy and subsequently received melphalan. The relative risk of ANL in patients who had ever been treated with both radiation and chemotherapy (ratio of observed to expected cancers, 120; 95 per cent confidence limits, 44 to 261) was slightly but not significantly higher than that in patients who were treated with chemotherapy alone (ratio of observed to expected cancers, 100; 95 per cent confidence limits, 37 to 218). The relative risks for patients who had ever been treated with melphalan and chlorambucil were 122 and 159, respectively. Among the 998 patients exposed to alkylating agents, the relative risk of ANL was 110 (95 per cent confidence limits, 56 to 191), the excess risk was 5.8 cases per 1000 women per year, and the cumulative seven-year risk was 9.6 ±3.3 per cent.

Evaluation of the risk of ANL as a function of *initial* drug dose in the three single-agent trials revealed that all cases of ANL occurred in the high-dose categories except for the case of one woman whose initial treatment was radiation therapy; she was treated subsequently with melphalan (Table 4). The absence of ANL cases in the Gynecologic Oncology Group Trial 2 is consistent with these observations, since that trial employed a very low cumulative-dose melphalan regimen (Table 1). The same pattern was observed when duration of treatment was considered. All 10 melphalan-related cases occurred in patients receiving 12 or more cycles of therapy, whereas the two chlorambucil-related cases developed in patients who received daily therapy for more than 18 months. Dose and duration of treatment were so highly correlated that separate effects of each could not be distinguished in this relatively small cohort.

Evaluation of the risk of ANL according to interval of observation indicated that all cases occurred two or more years after the diagnosis of ovarian cancer, with the last case developing seven years after diagnosis (Table 5). Only 84 patients were followed beyond seven years, precluding a meaningful estimate of cumulative risk at these longer intervals (Fig. 1). No significant differences in the risk of ANL were observed according to age at diagnosis of ovarian cancer, race, parity, menopausal status, stage, or cell type of ovarian cancer.

Discussion

This study demonstrates that there is an excess risk of ANL in patients with ovarian cancer who are treated with alkylating agents and that melphalan and

Table 3. Risk of Acute Nonlymphocytic Leukemia in Patients with Ovarian Cancer, According to Cancer Treatment.*

Postoperative Treatment (Ever Received)	No. of Patients	Woman-Years of Observation	Mean Follow-up	Acute Nonlymphocytic Leukemia					
				Observed	Expected	O/E	95% CL	Excess Risk (per 1000/year)	Cumulative Risk ±S.E. †
			yr						%
Observation alone	93	271	2.9	0	0.01	—	—	—	—
Radiation alone	308	1159	3.8	0	0.06	—	—	—	—
Chemotherapy alone	484	960	2.0	6	0.06	100	37–218	6.2	8.3±3.7
Radiation + chemotherapy	514	1068	2.1	6	0.05	120	44–261	5.6	12.1±6.3
Total	1399	3458	2.5	12	0.18	67	34–116	3.5	4.7±1.6
Alkylating agents ‡	998	2028	2.0	12	0.11	110	56–191	5.8	9.6±3.3
Melphalan ‡	773	1460	1.9	10	0.08	122	58–224	6.8	13.2±4.9
Chlorambucil ‡	71	263	3.7	2	0.01	159	18–574	7.5	5.7±4.0

*O/E denotes ratio of observed to expected cancers, and CL confidence limits. †At 7 years. ‡Includes patients who also received radiation therapy.

chlorambucil are two specific agents associated with this risk. The results indicate that treatment with radiation plus chemotherapy involves a risk of ANL that is indistinguishable from that observed with chemotherapy alone and provide some evidence for a dose-response relation.

A frequent criticism of previous studies of treatment-related cancers has been that tumor-registry incidence rates may not be appropriate to determine whether the incidence of ANL is excessive in a cohort of cancer patients — i.e., that the general population is not a proper comparison group in this setting. By making our observations within the framework of prospective, randomized clinical trials, we have circumvented this methodologic concern. The fact that all cases of ANL occurred in women who had been exposed to alkylating agents, whereas none developed in women who had been treated only with surgery or radiation or both, confirms the leukemogenic potential of these agents far more persuasively than could sophisticated statistical techniques. When rates of ANL in the general population were applied to our data, the risk of ANL was similar to previously reported estimates.[10,11] Furthermore, this association was not related to longer follow-up in women treated with alkylating-agent regimens, since the unexposed women were followed for a considerably longer time than were those receiving chemotherapy (Table 3). We have not used these data to assess survival as a function of therapy, since the five studies differed widely in design, eligibility criteria, stage of ovarian cancer studied, and duration of follow-up.

There can be no doubt that melphalan and chlorambucil are human leukemogens. The International Agency for Research on Cancer classified melphalan as "definitely carcinogenic in man" in 1979.[26] Our study is a formal, quantitative human survey in which the leukemogenic potential of this drug is objectively documented and quantified. Similarly, it is an analytic study of chlorambucil in which the index disease clearly lacks an intrinsic predisposition to ANL. These data, plus those derived from the evaluation of patients with polycythemia vera,[9] provide a firm basis for revising the classification of chlorambucil by the International Agency for Research on Cancer as only "probably carcinogenic in man."[27]

The similarity in risk of ANL between patients treated with chemotherapy only and those treated with both radiation and chemotherapy — in conjunction with the data of Reimer et al., which revealed no ANL excess in a much larger study group treated with radiation therapy[10] — strongly suggests that most if not all the excess ANL observed in patients with ovarian cancer treated with combined therapies is attributable to the alkylating agents. Our radiation-dosimetry data were not sufficiently detailed to compare radiation doses in the "radiation alone" subgroups with those in the combined-treatment subgroup. Current evidence indicates that the antimetabolites are not carcinogenic[27]; accordingly, we have assumed that 5-fluorouracil did not contribute to the risk of ANL in this study. The absence of a radiation effect may have been due to the administration of high doses of radiation to relatively small volumes of tissue, as reported in women irradiated for cervical cancer.[16] It has been suggested that under such circumstances, the irradiated bone marrow is destroyed; in contrast, lower-dose exposures are

Table 4. Observed and Expected Cases of Acute Nonlymphocytic Leukemia, According to Trial and Initial Chemotherapy Dose.

Trial and Initial Dose	No. of Patients	Observed	Expected	Observed/Expected	Rate/1000 Woman-Years
Princess Margaret Hospital *					
None	178	0	0.043	—	—
<2000 mg	30	0	0.004	—	—
≥2000 mg	37	2	0.009	222	10.6
M.D. Anderson Hospital †					
None	89	1 §	0.019	53	2.0
<700 mg	41	0	0.015	—	—
≥700 mg	42	4	0.011	364	17.7
GOG Trial 1 †‡					
None	123	0	0.019	—	—
<700 mg	43	0	0.007	—	—
≥700 mg	29	1	0.007	143	10.0

*Drug used was chlorambucil.
†Drug used was melphalan.
‡GOG denotes Gynecologic Oncology Group.
§This patient was subsequently treated extensively with melphalan (Case 7, Table 2).

Table 5. Observed and Expected Cases of Acute Nonlymphocytic Leukemia, According to Period of Observation after Diagnosis of Ovarian Cancer in Women Exposed to Alkylating Agents.

Observation Period	No. of Patients *	Woman-Years of Observation	Acute Nonlymphocytic Leukemia				
			Observed	Expected †	Observed/Expected	95% CL ‡	Rate/1000 WYO §
yr							
<2	998	1228	0	0.06	—	—	—
2–3	367	479	7	0.02	281	113–579	14.6
4–5	162	212	3	0.01	261	52–762	14.2
≥6	59	110	2	0.01	270	30–976	18.2

*Number of women starting the interval specified.
†Rounded off to two decimal places.
‡CL denotes confidence limits.
§WYO denotes woman-years of observation.

more likely to produce nonlethal marrow-cell injury, thereby increasing the risk of a carcinogenic mutation. It is conceivable that evaluation of a larger cohort of patients with ovarian cancer employing more sophisticated measures of radiation exposure might identify a radiation effect, but our data suggest that its contribution would be small in comparison to that of alkylating agents. Practically speaking, primary radiation therapy does not completely avoid the risk of ANL in patients with ovarian cancer, since, as illustrated by Case 7, many such patients subsequently receive alkylating agents.

Our data regarding dose-response relations arc limited yet valuable, given the paucity of such information in the literature. Nine of the 10 cases treated with melphalan received more than 700 mg — consistent with the data of Einhorn.[28] No cases of ANL occurred in the Gynecologic Oncology Group 2 trial, which employed an unusually low total dose of melphalan. Both the chlorambucil-related cases in our series received more than 2000 mg of drug. Finally, the risk of ANL in the three single-agent trials was confined to the highest initial dose levels (Table 4). Our data are too sparse to permit defining a safe dose; the lowest melphalan dose associated with ANL was 420 mg (Case 5, Gynecologic Oncology Group Trial 3). It is worth noting that the patients in our study in whom ANL developed were treated rather extensively with alkylating agents. Among the six patients who received only melphalan, the average dose was 1150 mg, and the mean number of cycles of treatment, 21. Whether restricting the dose or the duration of treatment or both would substantially reduce the risk of ANL is an important, unanswered question. Dose-response relations between therapy with alkylating agents and the risk of ANL have been suggested for patients with ovarian cancer treated with dihydroxybusulfan,[11] for patients with polycythemia vera treated with chlorambucil,[9] and for patients with non-Hodgkin's lymphoma receiving cyclophosphamide.[8] The available information suggests that the maximum total dose and duration of treatment should be considered in planning adjuvant-therapy trials that use alkylating agents.

A review of the literature revealed 58 patients in whom ANL developed after ovarian cancer[10,11] (a complete list of citations is available from us upon request). The mean age at diagnosis of ovarian cancer was 53 years, and the average latent period between diagnosis of ovarian cancer and diagnosis of ANL was 49 months. The majority of patients presented with advanced ovarian cancer (79 per cent), usually of the serous type (88 per cent). The mean survival after diagnosis of ANL was two months. Most patients acquired acute myelogenous leukemia (63 per cent); acute myelomonocytic and acute erythroid leukemia accounted for 13 per cent each. Of special note, 57 of the 58 patients were treated with chemotherapy; 27 received radiation therapy as well. Melphalan was the drug most commonly cited (36 per cent), followed by chlorambucil (23 per cent), thiotepa, and dihydroxybusulfan.

Melphalan and chlorambucil are mutagenic, clastogenic, carcinogenic, and immunosuppressive in various experimental systems.[1] In general, molecular data support the hypothesis that DNA is the critical target in alkylating-agent carcinogenesis and suggest that organ specificity may result from differences in the ability of various organs to repair the specific types of DNA damage caused by alkylating agents.[29] It is of interest that both melphalan and chlorambucil cause

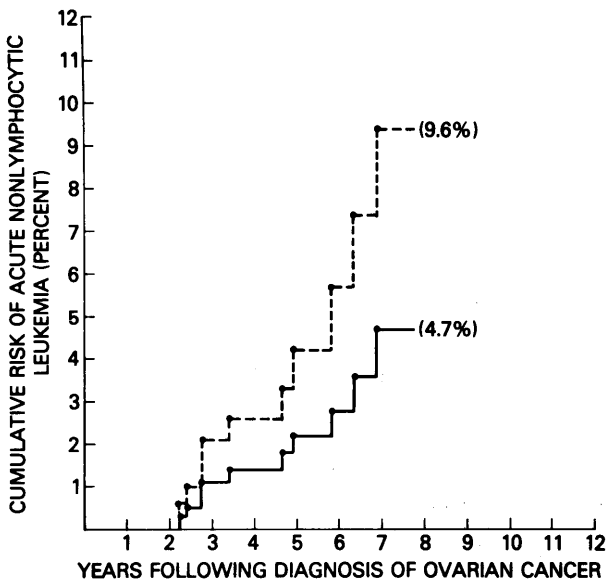

Figure 1. Cumulative Risk (Per Cent) of Acute Nonlymphocytic Leukemia after the Diagnosis of Ovarian Cancer.

Risks for the entire cohort of women with ovarian cancer are indicated by the solid line, and risks for women who were ever exposed to alkylating agents are indicated by the broken line. Although follow-up was continued for up to 11 years, the curves have been truncated at one year after the last case of ANL, since the absence of further cases of ANL may be the result of the small number of patients who were under observation for more than seven years.

persistent bone-marrow injury in mice, whereas other cytotoxic agents (e.g., cyclophosphamide) do not.[30] These data raise the possibility that some cytotoxic drugs may be less hazardous than others and indicate a need for more detailed studies of patients who have been exposed to other specific cytotoxic agents, as well as those who have been exposed to melphalan and chlorambucil in different schedules or for different durations of therapy.

Finally, what are the implications of these data for patient care? First of all, the benefit from melphalan and chlorambucil in patients with advanced ovarian cancer, in both improved survival and quality of life, is well documented.[17,18,31,32] In such patients, the risk of ANL should not be a deterrent to the administration of these agents. Late death from ANL in some patients is certainly preferable to early death from ovarian cancer in most patients. In fact, the overall contribution of ANL to mortality in a large cohort of women with advanced ovarian cancer may be negligible.[11] The issue is more complex when one considers administering these agents in an adjuvant fashion to cancer patients who are at low risk of relapse or to patients with non-neoplastic diseases in whom prolonged survival and prolonged therapy can be anticipated. In these patients, the risk–benefit assessment must give weight to the risk of late neoplastic complications of therapy, and epidemiologic studies of the type presented here can provide the quantitative information that is needed for such decision making. At the very least, the available data indicate that the dose and duration of use of alkylating agents should be kept to a minimum when the drugs are used in cancer patients at low risk of relapse or in patients with non-neoplastic diseases. Data of this type have already influenced the design of various adjuvant cancer trials and the treatment of patients with polycythemia vera.[9] Further work is needed to identify treatment regimens that maximize the benefit to the patient while minimizing the risk.

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