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Acute Myelogenous Leukemia as a Second Malignant Neoplasm Following the Successful Treatment of Advanced Hodgkin's Disease

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Of 209 Hodgkin's disease patients treated at least 6 months with a five-drug combination of induction chemotherapy and having a complete remission. four patients developed acute myelogenous leukemia (AML) as a second malignant neoplasm. The overall relative risk for development of AML is 185.0 ($P < 0.05$) and the mean time to Occurrence of AML is 5.3 years (median, 5.25 gears). H'hen examining patient subgroups, the highest relative risk noted was 338.5 ($P < 0.05$) for that group of patients receiving an additional 6 months of postinduction MOPP (nitrogen mustard, vincristine, procarbazine. and prednisone). Patients receiving only 6 months of induction BVCPP (BCNU, vinblastine, cyclophosphamide, procarbazine. and prednisone) had a relative risk of 166.2 ($P < 0.05$). These data results are consistent with previous reports that patients treated for Hodgkin's disease are at high risk for derelopment of AML. However, to date, no patients in this series have developed second malignancies other than AML.

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THE ADVANTAGE of combination therapy in prolonging survival in Hodgkin's disease patients has been adequately demonstrated.'.' The focus as of late has been on long term follow-up of patients achieving complete remission (CR) and the subsequent complications of their treatment. One of these complications. acute myelogenous leukemia (AML), is the subject of several reports. Cadman and associates[3] did a literature survey of 109 cases of AML following the successful treatment of Hodgkin's disease. Toland and coworkers' identified 11 cases of AML and several other tumors among 643 patients with all stages of Hodgkin's disease treated by members of the Southwest Oncology Group (SWOG) on three concurrently run protocols. The 11 AMLs all received some form of MOPP (nitrogen mustard. vincristine. procarbazine, and prednisone) therapy with or without radiation therapy. Their data basically support the conclusion of Arseneau and coworkers' that the intensity of the treatment significantly enhances the risk of development of a second malignancy. Valagussa and his associates[6] examined records of a total of 764 Hodgkin's disease patients treated with radiotherapy (RT), chemotherapy. or both. and reported a IO-year follow-up incidence of second solid tumors of 7.3%. and an incidence of 2.4% AMLs. Their AMLs occurred only after treatment with MOPP or modified MOPP regimens. Their highest incidence of leukemia **(5.4%)** occurred after treatment with extensive RT plus MOPP.

Glicksman and associates' analyzed data from 798 advanced Hodgkin's disease patients who achieved a CR on one of four Cancer and Leukemia Group B (CALGB) treatment protocols between 1966 and 1974. These patients had a mean follow-up of 46 months. Ten patients developed AML with a median time to development of 6 years. The relative risk (ratio of the rate of AML among those with Hodgkin's disease to the expected rate of AML in the general population) is 133. which is highly significant ($P < 0.001$). Boivin and Hutchison[8] reported on 1553 patients diagnosed with Hodgkin's disease during the period 1940 to 1975. The incidence of leukemia in the subgroup of patients with some form of combination chemotherapy and/or intensive RT (3000 rad or more to at least two of the following groups of lymph nodes:supradiaphragmatic. para-aortic. and pelvic) was 2.15. The relative risk of AML ranged from 40 for combination chemotherapy only to 290 for both chemotherapy and intensive RT.

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TABLE I. Patient Charactenstics

	No.	%
Total complete remissions	209	100.0
Sex		
male	135	64.6
female	74	35.4
Age (mean. 36 4)		
<30	93	44.5
30–49	64	30.6
≥50	52	24.9
Stage and symptoms		
2A	3	I.4
2B	3	I.4
3A	13	6.2
3B	89	42.6
4A	21	10.0
4B	80	38.3
Histologic features		
Lymphocyte depletion	16	7.7
Lymphocyte predominate	2	1.0
Mixed cell	44	21.1
Nodular sclerosis	121	57.9
Unspecified	26	12.4
Splenectomy		
Done	69	33.0
Not done	131	62.1
Unknown	9	4.3
Pnor therapy		
None	117	56.0
Radiotherapy only	64	30.6
Chemotherapy only	9	4.3
Radiotherapy and chemotherapy	19	9.I
Postinduction therapy		
BVCPP	37	17.7
MOPP	51	24.4
No therapy	58	27.8
Unmaintained	63	30.1
Volume of pnor radiotherapy		
Yone	126	60.3
involved field	12	5.7
Extended field	38	18.2
Total nodal	11	5.3
Data incomplete	22	10.5

BVCPP: BCNU. vinblastine. cyclophosphamide. procarbazine. and prednisone; MOPP: nitrogen mustard. vincristine. procarbazine. and prednisone.

In this report we assess the risk of developing AML in 209 advanced Hodgkin's disease patients achieving a CR on a Southeastern Cancer Study Group **(SECSG)** chemotherapy protocol. These data confirm the results of past studies in that patients receiving combination chemotherapy for a period of time (typically involving an alkylating agent and procarbazine) represent an exposed population of individuals who are at high risk of developing AML. Also. intensive follow-up, to date. of our series has not yet revealed any occurrence of a second malignant neoplasm other than AML.

Methods

Beginning in 1971 a total of 505 patients were entered on SECSG protocol 340 and treated with 6 monthly cycles (×6) of **BVCPP** (BCNU 100 mg/M^2 intravenously every 28 days × 6. vinblastine 5 mg/M^2 intravenously every 28 days × 6. cyclophosphamide 600 mg/m^2 intravenously every 28 days × 6. procarbazine 100 mg/M^2 daily orally × 10 every 28 days × 6 [reached by 50 mg increments], and prednisone 60 mg/M^2/daily orally × 10 every 28 days × 6). For a patient to be eligible it was necessary that the histology be confirmed by a Lymphoma Repository Referee and that the patient have either Stage III or IV disease, or have relapsed in an area previously treated with more than 3000 rad of radiation therapy. In a small number of instances, patients with earlier stage disease who had refused treatment with radiation were included. Staging was according to the Ann Arbor System, and was recorded as the point at entry into the study. Laparotomy was not required if Stage 3B or greater was clinically evident, or if relapse had occurred in an area of prior radiation therapy. Appropriate history and physical examinations were requried for all patients. Of the 341 eligible and evaluable cases. 209 (61%) patients achieved a CR. After stratification according to the amount of prior therapy the CRs were eligible for randomization to no additional therapy. 6 monthly cycles (X6) of MOPP, (nitrogen mustard 6 mg/M^2 intravenously on days 1 and 8 every 28 days × 6, vincristine 1.4 mg/M^2 [for a maximum of 2 mg] intravenously on days 1 and 8 every 28 days × 6, procarbazine 50 mg/M^2 on day 1, 100 mg on day 2, and 100 mg/M^2/daily orally on days 3-10 every 28 days × 6. and prednisone 40 mg/M^2/daily orally on days 1–14 every 28 days × 6), or 6 additional monthly cycles of BVCPP. The stratification divided patients according to whether they: (1) had received no prior therapy; *(2)* had received minimal prior therapy, defined as radiation less than 3000 rad to less than three portals and no combination chemotherapy (MOPP) or demonstrated resistance to single agent therapy: and (3) had major prior therapy, being more therapy than (2).

The incidence density is calculated by dividing the number of AMLs by the population-time (person-yean of observation). The relative risk (RR). also referred to as the incidence density ratio or risk ratio.' is the incidence density in the exposed population (Hodgkin's disease) divided by the incidence density in the unexposed population. This latter density is based on the age and sex-specific cohort from the Third National Cancer Survey conducted by the National Cancer Institute in 1969. Since the incidence data are reported by age groups. for each sex one has to add 1 year of age to a patient's on-study age for each year at risk or in follow-up on the protocol in order to appropriately calculate the RR. Also the 95% confidence limits" are calculated for each reported RR Another way of characterizing the occurrence of AML is by the life table estimate (LTE). which is simply the

chance of developing AML by a particular time during the follow-up period. In this study we compute the LTE for various subgroups of AML patients by the time of last procotol follow-up.

Results

The patient characteristics of the 209 CRs under study are given in Tables 1 and 2. The majority of patients had no prior therapy and were unmaintained following 6 induction courses of BVCPP (Table 2). All 209 patients achieved a CR within 12 months of starting therapy. Sinety-five percent of these achieved a CR by 6 months. The remaining 5% had their therapy delayed while their counts recovered. Patients with both major and minor prior therapy had approximately the same rate of time to achievement of CR. The influence of CR is seen as a favorable factor for survival prognosis.[1] A portion of these CRs represent a cohort of patients who. while possibly cured of their disease. can be expected to manifest some of the resultant morbidity associated with the achievement of that cure. Four of the 209 patients in this study were diagnosed as having developed AML with a median time to development of 5.3 years.

The RR for the total group of patients was 185 ($P < .05$) and the mean follow-up was 4.34 years with an LTE of 5.3%. Table 3 gives the RR with 95% confidence limits and the LTE for major patient characteristics. The 95% confidence limits in all instances do not include one. (A RR equal to one would indicate that the incidence of AML in the Hodgkin's CR group would be the same as the incidence of AML for patients in the expected population [those in the Third National Cancer Survey]). Since none of our confidence limits include the value one. we can be 95% confident that the incidence is greater in our cohort of patients than in the expected population. In several instances. especially where the observed number of AMLs is only one. we see that the confidence limits are very broad with a lower limit close to one. However, in all cases the incidence of AML in our observed sample was significantly greater ($P < 0.05$) than expected.

TABLE 2 Maintenance Therapy by Previous Treatment

	No prior Rx	Minimal prior Rx	Major prior Rx	Total
BVCPP	18	4	15	37
MOPP	28	2	20	50
No Rx	38	2	19	59
Unmaintained	33	3	27	63
Total	117	11	81	209

Rx. treatment

TABLE 3. Relative Risk and Life-Table Estimate for Major Patient Characteristics

Characteristics	Total evaluable	Mean follow-up (mo)	No. of AML's observed	RR	95% confidence limits	LTE
Stage						
2	6	41.6	*0*	*0*		
3	102	53.4	3	263.5	(54.2. 787.6)	7.9% ± 4.65
4	101	51.3	1	98.0	(1.3. 545.3)	2.20; ± 2.20
Symptom Class						
A	37	53.0	0	*0*		
B	172	51.8	4	255.1	(60.6. 576.3)	6.3% ± 3.20
Sex						
Male	135	54.8	3	180.7	(36.3. 527.9)	5.8% ± 3.44
Female	74	47.1	1	199.4	(2.6. 1109.7)	4.0% ± 3.92
Age						
<30	93	54.7	*0*	*0*		
30–49	64	51.8	1	213.6	(2.8. 1188.6)	2.6'5 ± 2.60
50–79	52	47.8	3	249.9	(50.2. 730.1)	16.7%± 9.89
Prior treatment						
No prior Rx	117	54.3	4	278.7	(75.0. 713.5)	8.5% ± 4.29
Rt only	64	44.6	0	*0*		
Chemo Rx	9	66.6	*0*	*0*		
Rt + Chemo Rx	19	56.5	0	0		
Postinduction Rx						
MOPP	51	54.5	2	338.5	(38.0. 1222.2)	8.1% ± 5.51
BVCPP	37	59.3	0			
None	121	48.8	2	166.2	(18.7. 600.1)	6.1% ± 4.52
T	209	52 05	4	185.0	(49.8.473.7)	5.3% ± 2.75

AML: acute myelogenous leukemia: RR: relative risk: LTE: life table estimate: Rx: treatment: Rt. radiotherapy: MOPP. nitrogen mustard. vincristine. procarbazine. and prednisone: BVCPP: BCNC. vinblastine, cyclophosphamide. procarbazine. and prednisone.

TABLE 4. Characteristics of AML Patients

	Patients			
	1	2	3	4
Sex	F	M	M	M
Age	37.9	55.8	63.6	73.4
Stage	3	4	3	3
Symptom class	B	B	B	B
Histologic type	NS	Unspecified	NS	MC
Splenectomy	Yes	Yes	NO	NO
Prior therapy	None	None	None	None
Postinduction Rx	MOPP + bleomycin	MOPP	No Rx	No Rx
Time from onstudy to AML (yr)	6.5	4.1	4.2	6.3

AML: acute myelogenous leukemia: NS: nodular sclerosis: MC: mixed cell: MOPP: nitrogen mustard: vincristine. procarbazine. and prednisone: Rx: treatment.

In Table 4 we summarize the characteristics of the AML patients. Three of the four were men (RR = 180.7) with a mean follow-up of 54.8 months, and a mean age of 64.3 years (RR = 239.9). All four patients had B symptoms (RR = 225.1) and three had Stage III disease (RR = 269.5). None of the patients had any significant prior therapy (RR = 278.7). Two of the patients had postinduction MOPP. One of these patients received added bleomycin. This group of patients receiving postinduction MOPP registered the highest computed RR of 338.5. In contrast, that group having no therapy beyond 6 months of BVCPP had an RR of 166.2. No patients received any preinduction or postinduction radiation therapy. The overall LTE for development of AML was approximately 5.3%.

The cumulative percent of AML in Hodgkin's disease patients while in continuous CR was 2% at 10 years. This is consistent with other series. *i.e.*, Toland and associates.[5] and Valagussa and associates.[6]

Discussion

Long-term complications of therapy for Hodgkin's disease have been recognized for the past several years. Other studies examining combinations of modalities have suggested that the intensity of treatment significantly enhances the risk of occurrence of a second malignancy.[4,5] Confirmation of the combined modality effect in our data is lacking, in that all four AML patients received no radiation therapy. In the series of Toland and coworkers[4] the highest risk of AML occurred in patients receiving intensive chemotherapy (at least 6 months) and intensive RT (total nodal or extended field). All four of the AMLs in our series could be classified as receiving intensive chemotherapy by the SWOG criteria. Two of these patients received mustard and nitrosourea-containing combinations of drugs. This BVCPP-followed-by-MOPP group of patients represented our highest risk group (RR = 338.5). A previous report by Glicksman and coworkers[7] has shown that patients on induction MOPP have a higher risk (RR = 255) for development of AML as compared with our BVCPP-induced patients (RR = 185).

As of our most recent follow-up. none of the patients in our analysis have presented with second malignancies other than AML. It may be too early to make definitive assessments of the status of non-AML malignancies, because they appear to occur in patients who Sustained a CR beyond 7 years.[7] Only 15% (32 of 209) of our patient sample are at risk in CR beyond 7 years.

Treatment for Hodgkin's disease gives rise to the occurrence of second malignant neoplasms. However, analysis of the results of all the series to date does not preclude the possibility that Hodgkin's disease itself is not a risk factor for second malignancies. Only long-term follow-up and analysis of data of patients with other diseases successfully treated with adjuvant therapy will allow us to possibly confirm the carcinogenic effect, if any, of the therapies being studied. Whether or not this is a direct effect or a result of the immunologic suppression of these agents"." is yet to be clarified.

In this report, as in others, we have focused on the intensity of treatment without particular attention to the duration of therapy. All four of the AML patients in this study have achieved a CR by 6 courses of therapy. Perhaps therapy for less than 6 induction cycles is warranted Instead, a better policy might be treatment until CR and then for a cycle or two afterwards. rather than for a specified number of induction courses.

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