

SECOND MALIGNANCIES FOLLOWING TREATMENT FOR HODGKIN'S DISEASE: A GREEK EXPERIENCE

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ABSTRACT

The risk and the type of second malignancies (SM) developing in 217 treated Hodgkin's disease (HD) patients were studied. The median age of the patients was 35 years (range 14-83) and the M/F ratio 1.8. Treatment consisted of radiotherapy alone (24 patients, 11%), chemotherapy alone (96 patients, 44.3%), or a combination of both modalities (43 patients, 19.8%), while 54 patients (24.9%) received salvage treatment. The median follow-up time was 67 months (range 12-224). Ten patients developed a SM with a 5-year and 10-year actuarial risk of 3.3% and 5.4%, respectively. There were 3 cases of ANLL and MDS (actuarial risk of 2.4% at 6 years), 1 case of non-Hodgkin's lymphoma and 6 cases of solid tumors (actuarial risk of 3.2% at 10 years). The risk of developing SM was higher in males and older patients (>40 years). SM represent a serious late side effect of successful treatment for HD. The possibility of developing a SM must be taken into consideration in the initial treatment of the disease.

Key words: Hodgkin's disease, treatment, second malignancies.

The possibility of developing acute non-lymphoblastic leukemia (ANLL), myelodysplastic syndromes (MDS), non-Hodgkin's lymphoma (NHL) and various non-hemopoietic cancers after successful treatment for Hodgkin's disease (HD) has been increasingly recognized during the past two decades.¹⁻⁶

The mutagenic effects of chemotherapy (CT) or irradiation (RT) have been cited as reasons for the excess risk. Some studies have shown that factors other than the treatment modality can be important in predisposing to ANLL or MDS. These include advanced age and stage of the disease, depressed cellular immunity and splenectomy.^{4,5}

Although RT did not contribute to the risk of secondary ANLL, it emerged as the primary risk factor for developing second nonhemopoietic malignancies.^{2,9}

In the present study we report our experience with the development of various secondary malignancies after treatment of Hodgkin's disease.

Materials and Methods

Between January, 1977 and December, 1991, 227 consecutive patients with HD were diagnosed and treated in our units. Ten patients were excluded from the study because of incomplete follow-up. The median follow-up time was 67 months (range 12-224 months).

The distribution of patient sex, age, disease stage and the incidence of HD histological subtypes are presented in Table 1.

Splenectomy was performed as staging procedure in 19 of the 217 patients.

Over the 16 years of the study, patients were

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Table 1. Characteristics of the patient population.

Characteristics	No.	Patients	%
Sex			
Male	140	64.5	
Female	77	35.5	
Age (years)			
15-40	134	61.8	
41-83	83	38.2	
Stage			
I	36 (30 I _A , 6 I _B)	16.6	
II	84 (40 II _A , 44 II _B)	38.7	
III	73 (29 III _A , 44 III _B)	33.7	
IV	24 (1 IV _A , 23 IV _B)	11.0	
Histology			
Lymphocyte predominance	8	3.7	
Nodular sclerosis	129	59.5	
Mixed cellularity	69	31.8	
Lymphocyte depleted	11	5.0	

treated according to the type of presentation and strategy in use at that time. The drug combinations employed were MOPP (mechlorethamine, vincristine, procarbazine, prednisone), C-MOPP (cyclophosphamide instead of mechlorethamine in MOPP), CIVPP (chlorambucil, vinblastine, procarbazine, prednisone) and the alternating regimen MOPP/ABVD (adriamycin, bleomycin, vinblastine, dacarbazine). Radiotherapy was given either as a mantle field or as an inverted Y field. In a few cases local RT was given.

Pathologic stages I_A and II_A were treated with RT alone. The majority of patients with large mediastinal disease received 6 courses of CT followed by irradiation.

Patients with stages II_B, III_A and IV_{A,B} were treated with chemotherapy. There were a few patients in these stages who received additional (mainly local) RT. Maintenance CT was not given.

Patients who relapsed after CT were treated with a variety of second-line regimens that often incorporated the nitrosourea lomustine (CCNU) and etoposide (VP₁₆). Of the 217 patients, 96 (44.3%) were treated with CT alone (41 received MOPP, 37 MOPP/ABVD, 10 C-

MOPP and 8 CIVPP). The combination of CT and RT was given to 43 (19.8%) patients (20 received MOPP+RT, 15 MOPP/ABVD+RT, and 8 patients CIVPP or C-MOPP and RT).

Radiotherapy as the only treatment was given to 24 (11%) patients (20 received mantle and 4 inverted Y fields). Lastly, 54 (29.2%) patients received salvage treatment with various regimens.

The actuarial risk of developing second malignancies (SM) was evaluated by the Kaplan-Meier method (1958), and statistical differences were verified by means of the log-rank test.

Results

A total of 10 SM occurred in the group of 217 patients during the following-up time, with actuarial risks at 5 and 10 years of 3.3% and 5.4%, respectively.

The clinical characteristics, time to development of a SM and the treatment given the 10 patients are presented in Table 2.

Three types of SM were observed:

1) two cases of ANLL and one case of MDS (myelopathies);

2) NHL (1 case). This was the only case of a SM that developed in a 37-year-old patient who had undergone staging laparotomy and was treated with mantle irradiation alone;

3) solid tumors (cases of non melanomatous skin cancers were excluded from the study). This group included one case with pancreatic carcinoma, one with cerebellar medulloblastoma and four cases with lung carcinoma. It is of interest to note that all our patients with lung cancer were tobacco users.

The cumulative risk of developing ANLL and MDS in this series was 2.4% at 6 years, while it was 3.2% at 10 years for solid tumors.

Neither the type and amount of treatment nor splenectomy was significantly correlated with the development of SM. In contrast, the risk of developing SM was affected by age and sex. Patients under 40 years old at the time of diagnosis of HD had an actuarial risk of SM of 1.6% and 14.5% at 10 and 15 years, respectively, whereas the corresponding figures for patients over 40 years were 12% and 29.6%.

Table 2. Second malignancies (SM) in patients with Hodgkin's disease.

Patient no.	Age/sex	Histological type and stage of HD	initial treatment	time from diagnosis to SM (months)	type of SM	present status
1	63/M	MC, I _B	MOPP/ABVD*	8	ANLL	dead
2	65/M	NS, III _B	MOPPx6 + RT	52	RAEB	Dead
3	37/M	NS, II _B	MOPPx6 + CIVPP x 3 > CR relapse > MOPP/ABVD*	70	MML	Dead
4	37/M	NS, I _A	RT (mantle)	148	NHL	Alive
5	72/M	NS, II _B	CIVPP X 6	74	Pancreatic Ca	Dead
6	18/M	MC, II _A	RT (local) + MOPP x 3 > CR relapse CIVPP x 6 > RT	141	Medulloblastoma	Dead
7	60/M	LP, II _A	MOPP/ABDV*	23	Lung Ca	Dead
8	47/M	MC, III _B	MOPP x 6	58	Lung Ca	Dead
9	60/M	MC, I _A	RT (mantle)	21	Lung Ca	Dead
10	59/M	NS, II _A	RT (mantle) > CR relapse > MOPP/ABVD*	167	Lung Ca	Dead

CR: complete remission; * 3 cycles of each regimen

These differences were statistically significant ($p<0.02$). Secondary tumors were observed only in males who had an actuarial risk of 8.5% and 28.4% at 10 and 15 years, respectively. This male predominance was also statistically significant ($p<0.05$).

All 10 patients were in complete remission from HD when they developed the SM.

Discussion

The development of SM in patients treated for HD has been reported in the literature. The cumulative incidence varies among large series, depending on the type of CT given, the combination of CT and RT, the patients' ages and the initial stage of Hodgkin's disease.^{1,2,4,7}

The reported incidence of ANLL or MDS following successful treatment of HD ranges from 1.7 to 8% and many studies show that chemotherapy regimens with alkylating agents and nitrosureas, as well as dose intensity greatly increase the risk of this consequence.

The concomitant administration of RT increases the risk of ANLL or MDS according to

some studies,^{1,8} while other investigators have shown that the risk of a second ANLL or MDS is unaffected by the combination of CT and irradiation.^{3,4,7}

The cumulative incidence of ANLL or MDS in our series was 2.4% at 6 years, similar to some studies^{4,6} but much lower than others.³ All our patients with second myelopathies (one ANLL and 2 MDS) had been treated with CT, and the one who developed chronic myelomonocytic leukemia had been heavily pretreated.

The explanation for the low incidence of second myelopathies in our series is not clear. However, a few comments can be reasonably made. The present study includes patients treated after 1977, when many questions related to the treatment of HD had already been answered. Therefore the usual treatment program comprised 6 courses of CT without maintenance treatment. Furthermore, many of the patients in the present series were treated with the MOPP/ABVD alternating regimen.

Non-Hodgkin's lymphomas have also been reported with an increased incidence (4 to 5%

at 10 years) in patients treated for Hodgkin's disease.^{1,7,9} In the present series we observed only one case of NHL that developed 12 years later in a patient with stage I_A HD who had been splenectomized at staging and treated with mantle irradiation. Although splenectomized HD patients have been considered at increased risk of developing SM, mainly ANLL,⁵ such an association was not found in our study.

As far as second solid tumors are concerned, the cumulative incidence in treated HD patients is approximately 10-13% at 15 years,¹⁰ and it appears that this risk continues to increase with time. The development of second solid tumors seems to be independent of the type of drugs included in the chemotherapy regimens. However, in many series these malignancies (lung cancer, sarcoma) were observed in patients who had received RT during the course of their treatment.¹⁰

A significant increase in lung cancers has been reported in treated Hodgkin's disease patients.⁶ The interval between diagnosis of HD and development of lung cancer varies from 1 1/2 to 24 years.⁶

Although other factors, mainly tobacco, may play an important role in this sequence of events, patients with supradiaphragmatic RT or combined modality treatment are at increased risk for developing lung cancer. Of the 4 patients with lung cancer in our series, two had received CT, one RT, and the fourth had undergone combined treatment.

The present study confirms advancing age as an important risk factor in developing SM.¹ The male predominance found in this study requires commenting since sex is not described as a risk factor in most studies. The majority of SM observed in our patients were solid tumors including 4 cases of lung cancer. Other factors,

in addition to the treatment given for HD, such as smoking, may play a role in the excess risk of SM. It is of interest in this respect that all 4 patients who developed lung cancer were smokers.

In summary, SM represent a serious late side effect of the successful treatment of Hodgkin's disease. The possibility of developing such neoplasias must be taken into serious consideration when planning the initial treatment of these patients.

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