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Second Malignant Neoplasms after Radio-Chemotherapy of Hodgkin's Lymphoma

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ABSTRACT

The objective of this study is to identify the second malignant neoplasms (SMNs) after treatment of Hodgkin's lymphoma (HL)in long-term survivors (LTS) of Hodgkin's disease (HD) patients who were regularly attending the pediatric oncology clinic of National Cancer Institute (NCI). 42 LTS were studied. During 3 years period, all patients subjected to through clinical history/ examination. Files were revised for date of diagnoses, original site(s), stage, histopathological subtypes and dose/ duration of therapy. Clinical examination was done with laying stress on blood pressure, pulse, chest & cardiac examination, visceromegaly and the presence of lymphadenopathy. Lab investigations included CBC, ESR and bone marrow aspirate &/or biopsy. Radiodiagnostic studies were done whenever indicated. One LTS had acute myeloid leukemia [AML] as a second malignant neoplasm.

Finally, the study documented the risk of secondary malignancy [AML] was one of the long-term sequelae of radio-chemotherapy in HD patients. Recommendations regarding the follow-up of therapy for HD and Screening for early detection of late effects were discussed. New strategies with reduction or elimination of radiation dose are needed for dealing with HD, especially in children.

Keywords: Hodgkin's disease/ second malignancy/Treatments

INTRODUCTION

Hodgkin's lymphoma occurs predominantly in young adults and is one of the most curable malignancies. With current treatment approaches, most patients achieve a lasting complete remission [(1)]. Survivors of pediatric and adolescent HD clearly represent a subgroup of patients at high- to very high risk of secondary malignancies (SM) [(2)],which remains a serious late effect of treatment [(1)].This is particularly true for those children treated many decades ago with predominantly radiation-based therapies; they show an approximately tenfold increased risk of developing a second cancer [(3,2)]. With extended follow-up beyond 10 years, treatment complications, predominantly SMNs emerge as leading causes of excess death [(4)]. *Mertens et al,(2001)*[(5)]found subsequent SMNs to be the second most common cause of death, and *Robertson et al, (1994)*[(6)]found them to be the third most common cause of death in survivors. Unfortunately, SMN-specific mortality is associated with both radiotherapy (RT) and chemotherapy (CTH) [(4)]. Factors that might contribute to the risk of an SMN include primary diagnosis, type of therapy received, time from initial diagnosis, and presence of genetic predispositions [(7,8,9)]. Survivors are at risk for developing SMNs including leukemia, sarcomas, breast, thyroid, gastrointestinal, and lung carcinoma [(10)]. An increased risk of subsequent leukemia [therapy -related myelodysplasia and acute myeloid leukemia (t-MDS/AML)] is well-documented after exposure to epipodophyllotoxins (topoisomerase II inhibitors) and alkylating agents [(8)]. Solid SMN risk is more closely linked to radiation (RD), particularly at higher doses. Over the past 40 years, treatment for children with HL has evolved from high-dose extended-field radiation(EFRT) to combined-modality therapy with CTH and low-dose involved-field radiation (IFRT). Such treatment

protocols have the theoretical benefit of diminished risk of solid SMN due to decreased radiation exposure [10]. In 1970, Stanford investigators pioneered a combined modality treatment protocol with low-dose IFRT and mechlorethamine, vincristine, prednisone, procarbazine (MOPP) CTH. Children treated on this protocol had secondary leukemias.A second protocol was initiated in 1982 combining alternating cycles of MOPP and doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) CTH with low-dose IFRT [10].*Chow et al, (2006)*[11]achieved excellent survival with minimal late toxicity with MOPP/ABV. Additionally, MOPP or COPP (mechlorethamine, cyclophosphamide, vincristine, procarbazine, prednisone) based regimens significantly increase the risk for secondary leukemias [12]. A dose-dependent relationship is noted with alkylating agents, which typically cause t-MDS/AML after latencies of 5–10 years [9].Classically, these alkylating-agents-related leukemias arise early (2 to 10 years, mean 7 years) after Hodgkin's treatment, show typical cytogenetical abnormalities (e.g. monosomy 5 or 7) and often develop as AML on the background of a myelodysplastic syndrome [2].

Radiation is a well-known risk factor for the development of SMNs, [3] with some of the most compelling evidence in survivors of HL following mantle radiation [8]. Ionizing radiation is associated with several types of cancer, with the risk being highest when the exposure occurs at a younger age [3]. The risk increases with the total dose of radiation [13,3]and with increasing follow-up after radiation [14]. Examples of radiation-associated tumors include breast [15], lung, and thyroid cancers [13], brain tumors [3], and osteosarcoma [16]. Female patients treated with mantle radiation before the age of 30 years are at a significantly higher risk of developing radiation-related breast cancer than those treated after age 30 [17,15]. An increased risk of developing thyroid cancer has been described after radiation therapy for several primary cancers, including Hodgkin's disease, acute lymphoblastic leukemia (ALL), and brain tumors, and after total-body irradiation for hematopoietic cell transplantation. Higher doses of radiation as well as exposure to radiation at a young age have been identified as risk factors, although a recent study demonstrated a threshold effect, with a decreasing risk at very high doses [13]. An increased risk for lung cancer (relative risk, of 2.6- to 7.0-fold) was observed following exposure to chest radiation, especially in patients treated for HL [18,9]. Late complications among HL survivors are of particular concern. Indeed, after 10 to 15 years of follow-up, mortality from HL among early-stage patients is exceeded by mortality from late complications [19]. The recognition of these risks has resulted in modification of CTH regimens and of radiation fields and doses [20].

The present study aimed to identify SMNs as sequelae of RT and/or CTH on HD-LTS regularly attending the pediatric oncology clinic of NCI, Cairo University, during 3 years period.

PATIENTS AND METHODS

The patients were 42 (33 males and 9 females) who completed therapy for HD and off therapy more than 5 years. Their ages ranged from 9-22 years with a mean of 14.9±3.4 years and median age of 15.5 years. The mean follow up time was 7.47±2.19 years [median 6.75 & 6.75 years].

All patients were subjected to:

Thorough clinical history/ examinations:

Files of the LTS were revised for the date of diagnosis and end of treatment, original site(s), staging, histopathological subtype and dose & duration of therapy. Clinical examinations included blood pressure, pulse, and chest/heart examination, visceromegaly and the presence of lymphadenopathy.

Laboratory investigations included:

CBC, ESR, and bone marrow aspirate and / or biopsy.

Radiodiagnostic studies:

(plain X-ray, abdominal sonography, and chest/ abdominal/ pelvic CT scans, and lymphangiography) were done whenever indicated.

Ann Arbor Stage/substage Classification for HD [21] was performed. Staging laparotomy was done in 15 LTS (5 were positive) to confirm the diagnosis and allow proper pathological staging.

Treatment modalities are illustrated in tables [1&2]. The chemotherapeutic regimens used alone or in combination were *MOPP,ABVD*, *OPPA* [Adriamycine, Vincristine, Procarbazine& Prednisone], *COPP*.

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 6.3.5. Mean and standard deviation was applied whenever indicated. [22]

Table (1): Treatment modalities in LTS

Type	No.	%	Total	%
Radiotherapy alone: (IF)			1	2.4
Chemotherapy alone:			11	26.2
MOPP	8	19.0		
MOPP + ABVD	1	2.4		
MOPP + Others	2	4.8		
Chemo-radiotherapy:			30	71.4
MOPP	12	28.5		
MOPP + ABVD	4	9.5		
OPPA	4	9.5		
MOPP + OPPA	2	4.8		
MOPP + OPPA + ABVD	2	4.8		
Other regimens	6	14.3		

Table (2): Radiotherapy schedule of LTS

Types of radiotherapy	No.	%	Dose of fractionated irradiation (Gy)
-Involved Field (IF)			
* Whole neck	18	58.1	25-40
* Mediastinal	3	9.7	22-26
* Inguinal	2	6.5	22-40
-Mantle	1	3.2	23.5
-Inverted Y (IY)	4	12.9	25-30
-Whole neck + Whole abdomen + IY	1	3.2	30 + 15 + 15
-Cranial irradiation + IY	1	3.2	24 + 25.2
-Whole neck + IY	1	3.2	34 + 36
Total	31	100	

RESULTS

The results of the present work are presented in tables (3-5):

The presenting stage of the disease was stage I & III (35.7% for each) followed by stage II. The predominant subtype of HD was mixed-cellularity (54.8%) followed by nodular sclerosis (21.4%)(Table 3).

Table (3): Clinical Characteristics and Investigations of HD patients

Items	No. (%)	Items	No. (%)
Stage:		***Pathology:***	
I	15 (35.7%)	**L.P**	7(16.7%)
II	10(23.8%)	**M.C**	23(54.8%)
III	15(35.7%)	**N.S**	9(21.4%)
IV	2(4.8%)	**U.N**	3 (7.1%)

L.P. = Lymphocytic predominance **M.C.** = Mixed cellularity **N.S.** = Nodular sclerosis **U.N.**=Unknown type

The mean values of 1st and 2nd hours of ESR were 35.95±40.15 & 53.19±37.72 respectively. Anemia was detected in 45.2% of patients. Leucopenia and Leucocytosis was encountered in 11.9 % and 9.5 % of patients (Table 4).

Table (4): Haemogram findings in LTS

Items	No. (%)	Mean ± SD
Hemoglobin		12.2 ± 2.1
low HB	19 (45.2%)	
Normal*	23 (54.8%)	
TLC:		8.8 ± 8.9
<4,000	5 (11.9%)	
>11,000	4 (9.5%)	
Normal**	33 (78.6%)	
Platelet:		287.4 ± 137.5
<150,000	3 (7.1%)	
Normal***	39 (92.9%)	

HB = Hemoglobin, **TLC** = Total leucocytic count.

*Normal hemoglobin: 3-12 years: 11-14 gm/dl, Adult male: 13-16 gm/dl and Adult female: 12-14gm/dl ** Normal TLC: 4,000-11,000/cmm, *** Normal platelet count: 150,000-400,000/cmm

Bone marrow (BM) aspirate was performed in 32/42 LTS (ten patients refused the procedure). Two patients (4.8%) showed hypo-cellular marrow (with normal haemogram), 8(19%) patients had hyper-cellular marrow (5 with normal haemogram, 1 with decreased TLC and 2 with decreased hemoglobin). BM aspirate was normal in the remaining 21 patients. Only one patient (2.4%) was found leukemic (AML), and died soon after diagnosis. The patient was an 18 years old boy, originally diagnosed as stage

IIIB-HD (mixed-cellularity), who received both CTH (MOPP + OPPA + MIME/Plational/Ara C) and RT (IF & inverted Y), and discontinued therapy for 9 years (Table 5).

Table (5): BM aspirate in LTS:

BM aspirate	Normo-cellular	Hyper-cellular	Hypo-cellular	Diseased (AML)	Refused patients
No	21	8	2	1	10
%	50.0%	19.0%	4.8%	2.4%	23.8%

DISCUSSION

Survival rates have greatly improved as a result of more effective treatments for childhood cancer. Unfortunately, the improved prognosis has resulted in the occurrence of late, treatment-related complications [23]. Curative therapy has been linked to an excess risk of developing SMNs, [4] particularly leukemias, breast, lung, and thyroid tumors [7,11]. The most significant risk factor for the development of second tumor was the extent of treatment for HD [24]. The limited incidence of second tumors, in the present study was attributable to the shorter follow-up time, and probably the use of less aggressive treatment. The AML and myelodysplastic syndromes are well-documented complication secondary to chemo-radiotherapy for HD [25]. In the present work, only one LTS had secondary AML found on routine bone marrow examination and died soon after diagnosis. The patient was an 18 years old boy, originally diagnosed as stage IIIB-HD (mixed-cellularity), who received both CTH(MOPP + OPPA + MIME/Plational/Ara C) and RT (IF &inverted Y), and discontinued therapy for 9 years. Early reports of leukemia risk rising and falling between 5 and 10 years after treatment continued to be supported [12,26,27].*Oberlin et al., (1992)*[28]reported one AML in a girl who was treated by MOPP + ABVD regimen. Also, *Hunger et al, (1992)*[29] reported a case of acute lymphoblastic leukemia [ALL] occurring as a second malignancy 9 years after finishing the treatment. Similarly, the patient was treated for a mixed-cellularity HD, with MOPP regimen plus RT to the left hemi-mantle and upper abdomen. In contrast, *Chow et al,(2006)*[11]have no cases of secondary leukemia at the time of data analysis, but they reported one case only out of 67 patients treated with three cycles of CTH and 15 Gy RT developed a secondary malignancy. The risk of developing a secondary AML or myelodysplastic syndrome after the treatment of HD mainly depends on the treatment strategy and certain host-related factors [older age at diagnosis, recurrence of HD, late stage presentation, and genetic susceptibility [12,26,30,31]. SMNs are among the most serious and life-threatening late adverse effects experienced by the growing number of cancer survivors worldwide and are due in part to RT [32].Radiation therapy, when used alone, was associated with the lowest risk, but with a dose-related increase of risk [12,26]. Combination MOPP-CTH plus irradiation had the highest risk, with the risk of MOPP-CTH alone being in between [26].Other significant factors for developing leukemia include; 1st year treatment with CTH, follow-up treatment with CTH [30]. Splenectomy and probably splenic irradiation may also add to the risk therapy [12,26,30],although no significant correlation between splenectomy and the development of AML was found in another study [33].In contrast, *Franklin et al,(2006)*[1] reported that, RT as a first-line treatment strategy for stage I–III patients leads to a higher overall rate of all SM, solid tumor and NHL, respectively, than a combined modality strategy. He attributed that; this may be due to the significantly greater rate of progression/relapse and therefore intensive salvage therapy after RT alone. Also, Administration of RT in addition to CTH in first-line treatment of advanced-stage patients appears to increase the overall rate of all SM and acute leukemia, respectively. Additionally, *Koshy et al 2012*[34] examined the role of RT in stage I and II HD and

revealed a survival benefit with the addition of RT with no increase in secondary malignancies compared to patients who did not receive radiation therapy, by doing one of the largest studies. Furthermore, this nationwide study revealed an over 20% absolute decrease in the utilization of RT from 1988–2006.

In LTS, continuously free of HD, the cumulative probability of second leukemia is low, far less than that of second tumor [26]. Moreover; treatment regimens introduced in the 1980s have much lower leukemia risk than patients treated in the earlier years [30]. Even after autologous stem-cell transplantation for HD, the risk of secondary myelodysplasia or AML is not significantly increased whereas an increased risk of solid tumors exists [35]. Additionally, patients who received radiation therapy were more likely to develop secondary solid malignancies while those that did not receive radiation had a higher incidence of developing secondary leukemias [34]. Alternatively, *Hunger et al, (1994)*[36] reported up to 6.5% 10 years risk of 2ry leukemia, after 6 cycles of MOPP-CTH and 15-25 Gy irradiation. In the present study, the case of AML represented 2.4% of the study group. In accordance, *Bhatia et al., (1996)*[37] reported 24 cases of AML [24/ 1380(1.7%)] among 88 cases of SMN [6/88 (6%)]. Meanwhile, *Sankila et al., (1996)*[38] reported 62 SMN out of 1641 HD-LTS (3.8%), with 7 cases of leukemia [7/1641 (0.4%)]. In spite of an impressive reduction in chemo- and radiotherapy intensity, no negative impact was found on 10-year EFS or OS (88 vs 94%) and only 4(3.5%) out of 116 survivors developed a SMNs after a median follow-up of 8.5 years [11,2]. Thus, with the extended follow-up, and after a relatively short latent period, the cumulative incidence of leukemia rose sharply but appeared to reach a plateau after 14 years from diagnosis [15], or 2.8% at 15 years, while the incidence of solid second tumors (mainly lung, breast cancer and soft tissue) reaches 15% after 20 years [24,39,40,31], and approached 23.5% at 30 years from diagnosis [15]. The median interval to diagnosis of a SM is shortest for leukemia (4.3 years) and longest for lung cancer (18.4 years). *Mauch et al., (1996)*[24] reported 8 AML [out of 72 SMN], 10 non- Hodgkin's lymphoma [NHL] and 53 solid tumors, after a median time of 5, 7.25, 12.2 years respectively of treated HD. On the other hand, NHL has been reported at the immediate onset of CTH [41] or as late as 11 years after complete remission of HD [42]. Additionally, patients with HD appear to be at increased risk for NHL of the CNS (large-cell immunoblastic, of B-cell origin), which may be of poor prognosis [41]. Significant risk factors for NHL are older age, male sex and combined modality treatment [30]. A modestly increased risk for secondary gastrointestinal cancer (stomach, pancreas and small intestine), urogenital cancer and soft tissue sarcoma has also been reported [30,43], especially after combined modality therapy and treatment at young age. The risk is significantly elevated after 10 years and was highest >20 years after treatment [43]. Relapse of HD also increases the risk for SM [44]. Following RT, the predictive factors for a second cancer are age at diagnosis (<30 years), treatment for recurrent lymphoma and primary treatment without splenectomy. The risk of lung cancer is strongly related to RT [30]. Moreover, the majority of second cancers arise within or next to the irradiated portals, particularly breast cancer in females treated with mantle-field irradiation, between the ages of 10 and 25 years [30,27,40]. Irradiation doses of 35 Gy is still associated with a 10% incidence of SM after a median follow-up of 110 months [45]. Survival following development of a SM is poor in patients with leukemia, GIT tumors, lung cancer and sarcoma. Survival after other malignancies, including NHL, breast cancer is more encouraging [24].

Finally the present study concluded that, after a mean follow-up time of 7.47 ± 2.19 years, there is a significant risk of a secondary malignancy (AML). It has been demonstrated quite conclusively that LTS of childhood cancer carry a high burden of morbidity, with one third of survivors reporting severe or life-threatening complications 30 years after their primary diagnosis [46]. Attention now needs to focus on anoverall reduction in morbidity and mortality, by anticipating and preventing late complication, and an ultimate improvement in the overall quality of life of childhood cancer survivors [47]. Future therapeutic protocols for pediatric patients with HL should

pursue radiation dose reduction or elimination of radiation when feasible. Improved understanding of genetic predisposition and modifying factors and the impact of specific CTH agents will help to identify those patients at greatest risk of SMN [10].Recommendations include monitoring with an annual CBC for 10 years after exposure to alkylating agents or topoisomerase II inhibitors. Most other subsequent malignancies are associated with radiation exposure. Screening recommendations include a careful annual physical examination of the skin and soft tissues in the radiation field, with radiographic or other cancer screening evaluations as indicated.

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