

## Treatment of Lymphoid Malignancies in Patients With Ataxia-Telangiectasia

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**Background.** Patients with ataxia-telangiectasia (A-T) are at an increased risk for developing lymphoid malignancies, yet the appropriate therapy remains unknown. Radiation therapy at conventional doses results in destruction of normal tissue, which has suggested that full-dose chemotherapy might result in unacceptable toxicity in A-T patients with cancer. **Procedure.** The medical records of 412 A-T patients were reviewed to identify those patients who developed lymphoid malignancies and to analyze the type and duration of therapy, events during therapy, and off-therapy follow-up. **Results.** Of 74 A-T patients with lymphoid malignancies, 32 patients received chemotherapy. The 21 patients treated with standard chemotherapy had a significantly better median survival (9 months, range, 1-162+ months vs. 5 months, range, 0.5-28 months) ( $P = 0.03$ ) and complete remission rate (76% vs. 9%) ( $P = 0.001$ ) than the 11 treated with reduced dose chemotherapy. Three of the 21 full-dose

chemotherapy patients required dose reductions because of neutropenia. Seven of the 14 patients exposed to 1,200 mg/m<sup>2</sup> or greater of cyclophosphamide developed hemorrhagic cystitis. All three patients exposed to bleomycin developed pulmonary disease which was fatal in two. Of the 16 standard-dose chemotherapy patients who achieved a complete remission, two remain disease-free, five have died of recurrent disease, and five died of pulmonary disorders and four of other causes while in remission. **Conclusions.** Standard-dose chemotherapy should be given to each A-T patient with a lymphoid malignancy unless additional physical or emotional problems make it unlikely that the patient will benefit. Morbidity and mortality may be reduced by prophylaxis against hemorrhagic cystitis and early detection and treatment of pulmonary disorders. *Med. Pediatr. Oncol.* 31:491-497, 1998.

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**Key words:** Hodgkin disease; non-Hodgkin lymphoma; Ataxia-telangiectasia; cancer therapy

### INTRODUCTION

Ataxia-telangiectasia (A-T) is an autosomal recessive multisystem syndrome in which the incidence of cancer is elevated approximately 100-fold [1]. Acute leukemias and lymphomas are the predominant cancers in children with A-T [1]. Although the A-T gene has been cloned and sequenced [2], the mechanisms by which A-T homozygotes and heterozygotes are predisposed to cancer are still unknown.

It is well established that radiation treatment of A-T patients at conventional doses leads to serious, often fatal, destruction of normal tissues [3]. The mechanism of radiation sensitivity in A-T is unknown, although it is hypothesized that the failure of A-T cells to recognize radiation-induced DNA damage at cell cycle checkpoints plays an important role [4]. It is believed that mutations at the A-T locus make cells more vulnerable to oxidative damage induced by ionizing radiation [3] or radiomimetic drugs such as bleomycin [5].

Reduced dose (RD) radiation treatment has been associated with prolonged survival in one A-T patient with lymphoma [6]. Although there is no evidence that standard dose (SD) conventional chemotherapy for lymphoid cancer in A-T patients produces excess harmful side effects, RD chemotherapy has been recommended in this setting [6,7].

We reviewed the clinical charts of 412 A-T patients collected from the A-T registry to determine the effects of radiation therapy and cancer chemotherapy on A-T patients.

### PATIENTS AND METHODS

Medical records were collected through a comprehensive search for all cases of A-T in the United States under a protocol approved by the committee on the protection of human subjects at New York Medical College. Records were compiled after an extensive letter writing effort to pediatric neurologists, pediatric immunologists, medical geneticists, cerebral palsy centers, and the Immunodeficiency Cancer Registry in the United States in which we asked for referral of all patients with A-T. A-T patients with cancer were not sought specifically, since

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oncologists were not surveyed in collecting these patients. Medical records were collected from all hospitals, clinics, physicians, and other health professionals who had cared for these patients after written informed consent was obtained. Several families who learned from other sources that we were studying A-T volunteered to participate in our study. A-T was diagnosed if the medical records confirmed that the patient had progressive cerebellar ataxia, oculocutaneous telangiectasia, and, when available, an abnormal serum alpha-fetoprotein. Some of the patients included in this study have already been reported in a previous paper [1] and case report [6].

The records of all patients with lymphoid malignancies were reviewed for date of diagnosis, type and duration of therapy, events during therapy, and off-therapy follow-up. The treating physicians were contacted for all data that were missing from the records already collected. We considered that a patient received SD chemotherapy if s/he was treated according to a standard cancer chemotherapy protocol or the records documented doses equal to those given under the cancer chemotherapy protocols in contemporary use at the time of diagnosis (asparaginase, 6,000 U; bleomycin, 10 U; chlorambucil, 6 mg; cyclophosphamide, 1,200 mg; cytarabine, 100 mg; dacarbazine, 375 mg; etoposide, 100 mg; mercaptopurine, 75 mg; methotrexate, 15 mg; prednisone, 40 mg; procarbazine, 100 mg; vinblastine, 6 mg; and vincristine, 1.5 mg, all doses are per m<sup>2</sup> of body surface area). A patient was considered to have received RD chemotherapy if the medical record indicated that the physician decided to administer doses lower than best clinical practice at the time, and such doses were documented in the record.

### Statistical Analysis

Survival curves were estimated according to the Kaplan-Meier method and compared by the log-rank test. Fisher's exact test was performed to assess the difference in response rates between SD and RD chemotherapy. The statistical analyses were performed with Statistical Package for the Social Sciences software. The statistical methods cannot adjust for possible selection bias as to which patients received standard doses and which received reduced doses of chemotherapy.

### RESULTS

We reviewed the medical records of 412 A-T patients and identified 74 (18%) who had lymphoid malignancies (Table I). Seven of these patients with lymphoid malignancies also had solid tumors (Table II). In six patients, the diagnosis of the solid tumor preceded the diagnosis of the lymphoid tumor. One patient had an occult thyroid papillary carcinoma discovered at autopsy. The solid tumors were surgically resected whenever possible.

TABLE I. Malignancies in A-T Patients

Lymphoid tumors (n = 75)	n (%)
NHL	48 (64)
Acute leukemia	11 (15)
Hodgkin disease	10 (13)
Chronic lymphocytic leukemia	3 (4)
Lymph node cancer (NOS)	1 (1)
Sezary syndrome	1 (1)
Waldenstrom macroglobulinemia	1 (1)

TABLE II. Solid Tumors in A-T Patients With Lymphoid Malignancies

Lymphoid tumor	Solid tumor(s)
Chronic lymphocytic leukemia	Uterine leiomyosarcoma Ovarian cystadenofibroma
Chronic lymphocytic leukemia	Uterine leiomyoma
Sezary syndrome	Uterine fibroid
Large cell lymphoma	Bladder papillary cell carcinoma Thyroid follicular cell carcinoma
Large cell lymphoma	Right femoral osteochondroma
Large cell lymphoma	Parotid mucoepidermoid carcinoma
Lymphoma	Thyroid papillary carcinoma

Twenty-four patients were excluded for the following reasons: 16 patients with lymphoid malignancies had only death certificate information available and 8 patients had their disease discovered only at autopsy.

Five patients with lymphoma, two with acute lymphoblastic leukemia (ALL), and one each with chronic lymphocytic leukemia and Hodgkin disease were not given therapy and had a median survival of 2 months (range, 0-10 months). The decision not to treat these patients was based solely on the patient's, physician's, and family's perception that there are potential excess therapy-related toxicities for A-T patients. In some cases, the patient's underlying disease, A-T, was simply regarded as a contraindication to treatment.

Six lymphoma and two Hodgkin disease patients received radiation therapy only and had a median survival of 3.5 months (range, 1-7 months). One of these lymphoma patients achieved a complete remission after 14 fractions of Cobalt-60 irradiation (total dose 2,300 cGy) and died in remission 6 months after diagnosis. This patient suffered severe esophagitis and required a gastrostomy tube for feeding. One patient with an ileocecal lymphoma treated with surgery alone was event-free for 46 months until recurrence.

Thirty-two patients with lymphoid malignancies received chemotherapy as shown in Table III. The study population (n = 32) was treated between 1962 and 1996: one during the 1960s; eight during the 1970s; 21 during the 1980s; and two during the 1990s. There were no discernible differences in clinical status and stage of disease between the patients receiving SD (n = 21) or RD chemotherapy (n = 11). There were 23 patients with high-grade non-Hodgkin lymphoma (NHL) [8] (11 with

TABLE III. Patients Characteristics\*

Diagnosis (stage)	Age (years)	Year of diagnosis	Chemotherapy	Survival (months)
SD chemotherapy (achieved complete remission)				
NHL (B I)	6.5	1981	COP	162+
NHL (Lymph III)	17.5	1991	OAr-a-cTG	43+
NHL (B I)	9.8	1977	COP	108
NHL (B I)	9.5	1971	COP	82
NHL (LC I)	17.1	1983	CHOP	62
NHL (B I)	9.1	1986	COVM	58
NHL (B II)	14.8	1982	CHOP	52
NHL (LC IV)	22.8	1968	CHOP	6
NHL (LC IV)	7.0	1977	OP	5
NHL (LC IV)	11.3	1989	CHOP	4
NHL (NOS IV)	35.6	1996	CHOPB	2
NHL (LC I)	18.2	1987	CHOP	1
ALL	14.2	1978	POD	46
ALL	3.1	1978	POLasP	22
ALL	14.7	1980	PODLasp	12
ALL	8.8	1968	PO, 6-MP	6
SD chemotherapy (no remission)				
NHL (LC II)	13.3	1982	COP	22
NHL (Lymph IV)	21.1	1983	CHOP	5
NHL (B II)	4.5	1977	CP	5
NHL (LC IV)	26.3	1962	CHVP	4
NHL (B IV)	5.0	1981	COP	1
RD chemotherapy				
NHL (Lymph III, CR)	12.2	1984	COP	15
NHL (LC III)	13.0	1984	OH	9.5
NHL (B IV)	17.5	1988	CHOP	5
NHL (LC IV)	8.3	1985	HOP	2
NHL (LC I)	25.0	1985	M	0.5
NHL (LC IV)	23.6	1979	CO	11
HDNSIVB	15.6	1989	P, VP	28
HDNSIIB	5.7	1985	HOP/ChVPPr	17
HDLDIVB	12.3	1984	ABVD	4
HDLDIVB	20.5	1986	ABVD	3
ALL	19.7	1970	P	2

\*CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CHOPB, cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin; COP, cyclophosphamide, vincristine, prednisone; CO, cyclophosphamide, vincristine; CHVP, cyclophosphamide, doxorubicin, etoposide; HOP, doxorubicin, vincristine, prednisone; COVM, doxorubicin, vincristine, vinblastine, methotrexate; OAr-a-cTG, vincristine, cytarabine, thioguanine; OH, vincristine, doxorubicin; OP, vincristine, prednisone; M, methotrexate; PODLasP, prednisone, vincristine, daunomycin, asparaginase; P, prednisone; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; VP, P, etoposide, prednisone; HOP/ChVPPr, doxorubicin, vincristine, prednisone/chlorambucil, vinblastine, prednisone, procarbazine; CR, complete remission; B, Burkitt; LC, large cell; Lymph, lymphoblastic; HDNS, Hodgkin disease with nodular sclerosis; HDLD, Hodgkin disease lymphocyte depleted.

large cell, 8 with Burkitt, 3 with lymphoblastic, and 1 not otherwise specified [NOS]), 5 with ALL, and 4 with Hodgkin disease with a median age at diagnosis of 13.3 years, 11.5 years, and 13.9 years, and a median survival of 6 months (range, 0.5–162+ months), 14 months (range, 2–46 months), and 10.5 months (range, 3–28 months), respectively.

Four of the five leukemia patients would be classified as standard-risk and the other as high-risk (leukocytosis) using contemporary criteria [9]. The four standard-risk

patients received SD chemotherapy and all achieved a complete remission. The high-risk patient was treated in 1970, received only prednisone, and did not achieve a remission. Although each of our four Hodgkin disease patients presented with high-risk stage (Table III), none had bulky adenopathy.

There was heterogeneity in the chemotherapies received: 29 of the 32 patients were not enrolled on cancer chemotherapy protocols. Eighteen patients received SD chemotherapy and three (two with ALL and one with

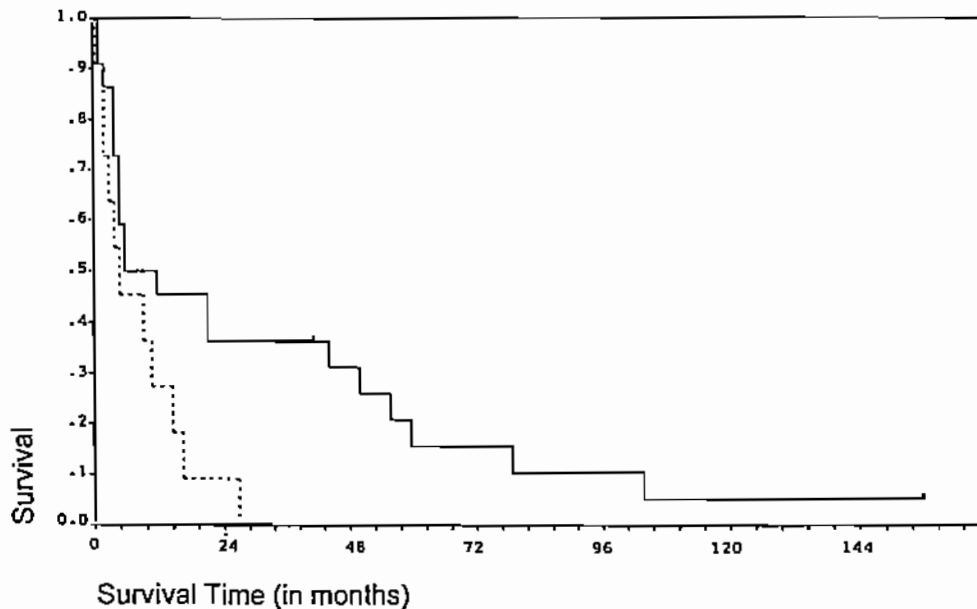


Fig. 1. Overall survival of patients treated with SD (straight line) or RD chemotherapy (dashed line).

NHL) were treated on cancer chemotherapy protocols. Eighteen of these 21 patients completed the treatment course. Eleven patients received RD chemotherapy ranging from 33% to 75% of SD from the initiation of treatment because of their physicians' and families' concern about possible excess chemotherapy-related toxicity in A-T patients. Each of the 11 medical records documented the intention to treat at a reduced dose.

The median survival of the 21 patients receiving SD chemotherapy (12 months, range 1–162+ months) was significantly better than that of the 11 patients receiving RD chemotherapy (5 months, range 0.5–28 months) (Fig. 1) ( $P = 0.03$ , log-rank analysis). One RD chemotherapy patient and 16 of the 21 SD chemotherapy patients achieved complete remissions ( $P = 0.001$ , Fisher's exact test).

The median survival of the 16 complete remission patients (32.5 months, range 1–162+ months) was significantly better than the median survival of the 5 patients who did not achieve a complete remission on SD therapy (5 months, range 1–22 months) ( $P = 0.01$ , log-rank analysis) and the median survival of the 11 who received RD chemotherapy (5 months, range 0.5–28 months) ( $P = 0.006$ , log-rank analysis). Five patients with NHL and four with ALL were treated prior to 1980. Six achieved a complete remission and three did not, with a median survival of 34 months (range 5–108 months) and 5 months (range 2–11 months), respectively. Eighteen patients with NHL, four with Hodgkin disease, and one with ALL were treated after 1980. Eleven patients achieved a complete remission and 12 did not with a median survival of 15 months (range 1–162+ months) and 4.5 months (range 0.5–28 months), respectively. There were no significant differences in

complete remission rate ( $P = 0.71$ , Fisher's exact test) and overall survival in those achieving a complete remission ( $P = 0.85$ , log-rank analysis) between the patients treated in these two time periods.

At present, 2 of the 16 complete remission patients are disease-free (43+ and 162+ months). Five patients have died of recurrent disease at a median of 22 months (range 5–61 months) after achieving a complete remission. Three of the five had ALL, one had a stage I NHL of the Waldeyer ring, and one had a cervical large cell lymphoma. Two of the leukemic patients had a clinical bone marrow relapse, while the third died from varicella and had his relapse (testes and meninges) discovered only at autopsy. One leukemic patient achieved a second remission with vincristine and prednisone. A second bone marrow relapse after 3 months in second remission was refractory to therapy. Each of the lymphoma patients suffered local recurrences.

Nine patients died without evidence of a lymphoid malignancy at a median of 6 months (range 1–108 months). Five patients died of pulmonary disease. Three patients had evidence of pulmonary disease manifesting as chronic infiltrates, pneumonia, or tachypnea prior to their cancer diagnosis. Two patients developed lung disease after the diagnosis of cancer. One patient developed an acute onset of tachypnea and the presence of rales and a pleural friction rub on auscultation. Chest x-ray revealed interstitial infiltrates and a left pleural effusion. The patient died of respiratory failure due to either an infection or pulmonary embolus. The other patient developed a cough and pneumonitis during therapy and died of an acute fungal bronchopneumonia. The four remaining patients died: 1) at the time of diagnosis from sepsis, 2) from a massive hemorrhage after a liver biopsy,

3) from congestive heart failure after a massive gastrointestinal hemorrhage, and 4) from sudden cardiorespiratory arrest with the cause not identified at autopsy.

Three patients required dose reductions during therapy because of neutropenia (two with ALL and one with NHL). Seven of the 14 patients (50%) exposed to 1,200 mg/m<sup>2</sup> or greater of cyclophosphamide developed hemorrhagic cystitis. Pulmonary or cardiac signs of cyclophosphamide-related toxicity were not observed. The three patients exposed to less than 1,200 mg/m<sup>2</sup> of cyclophosphamide did not develop cystitis. All received intravenous hydration to achieve a supraphysiologic urine output, but none received the uroepithelial protectant mesna. Three patients had severe complications following hemorrhagic cystitis that required urologic intervention. Urinary tract infections or concomitant abdominal/pelvic irradiation was not documented in any of the seven cases.

One lymphoma patient received the usual dose of bleomycin (10 μm<sup>2</sup>) and two Hodgkin disease patients received 3/4 and 1/3, respectively, as part of the ABVD regimen. The patient given 1/3 the usual dose of bleomycin had no unusual respiratory symptoms but was noted to have fine nodules throughout her lung at autopsy. However, the patient given 3/4 the usual dose of bleomycin developed progressive pulmonary fibrosis, which caused his death. The patient given 10 μm<sup>2</sup> of bleomycin developed rapidly progressive pulmonary deterioration and died 2 months after diagnosis. Signs of vincristine or doxorubicin toxicity were not observed in patients given these drugs.

## DISCUSSION

Chemotherapy of lymphoid malignancies has changed in recent decades, as new drugs, new combinations of drugs, and new treatment schedules have been introduced after careful studies demonstrating their safety and efficacy [10,11]. Thus, the SD regimen for chemotherapy of lymphoid cancers in general has changed over the years. Many A-T patients with lymphoid cancer have been treated with chemotherapy as if they were similar to cancer patients in the general population. Others have received chemotherapy on schedules in which the dose intensity and total cumulative doses were reduced because of fears that A-T patients suffer excess side effects from conventional doses. The present data show that A-T patients had a higher remission rate and longer survival when treated with SD rather than RD chemotherapy. This conclusion is supported by the recent report of a 22-month-old A-T patient treated with SD chemotherapy for a T-cell leukemia who is alive in first clinical remission 4 years after diagnosis [12]. However, it remains to be determined which regimen, if any, is superior in A-T patients with lymphoid cancer.

Three of 22 patients who received optimal chemotherapy required dose reductions because of myelosuppression. This proportion of patients is comparable to that observed in general oncology practice [13].

It is not clear that A-T patients with lymphomas benefit from radiation therapy in addition to chemotherapy. In four series [14–17], chemotherapy alone has been shown to be as effective as chemotherapy combined with radiation in treating NHL patients from the general population. Conventional wisdom states that there is probably no routine indication for radiation in pediatric NHL, and its use should be reserved for exceptional circumstances [18]. However, the two patients in our series who received radiation, one as an emergency and the other at reduced doses, achieved a complete remission and one remains alive event-free.

In this series, 7 of 14 (50%) patients exposed to 1,200 mg/m<sup>2</sup> or greater of cyclophosphamide suffered hemorrhagic cystitis, with serious complications in 3 patients. Alternative explanations or etiologies for the cystitis were not found. Mesna, which protects the uroepithelium from acrolein-induced damage [19], was not administered to any patient in this series.

Moderate to severe lung toxicity was observed in the three patients in this series exposed to bleomycin. In two of these patients, rapid pulmonary deterioration resulted in death. Such lung complications were not observed in two reported A-T patients with Hodgkin disease exposed to 3/4 the usual bleomycin dose, although details of chest x-rays or lung pathology were not available [7]. Oxidant injury to pulmonary capillary endothelium is the main mechanism of bleomycin toxicity [20]. Moreover, previous oxygen or radiation exposure may enhance the development of toxic pulmonary reactions [21]. Bleomycin has the same effect on cultured A-T homozygous cells as ionizing radiation [22, 23].

The cancers in five patients relapsed after achieving a complete remission. The three leukemic relapses all occurred while the patients were still receiving therapy. Two lymphoma patients suffered disease recurrences 51 months after completing therapy. Since most relapses in high-grade NHL occur within 24 months of achieving remission, it is possible that these recurrences represent second de novo lymphomas as opposed to regrowth of the original lymphoma. In fact, the occurrence of independent solid tumors in seven patients with lymphoid malignancies (Table II) suggests that A-T patients may have multiple primary tumors.

## RECOMMENDATIONS

Physicians have withheld or reduced cancer chemotherapy because of the perception that the drugs used might be excessively toxic in A-T patients and that these patients have a very limited lifespan and poor quality of

life. However, many A-T patients survive until their 30s or 40s. These patients often have a remarkably good quality of life despite their neurologic disability because of strong family support and the warm personality, resourcefulness, and excellent sense of humor often observed in A-T patients. The present series suggests a cautious trial in A-T patients of more aggressive chemotherapies that have been shown to be of value in cooperative group studies.

The need for radiation therapy in advanced stage Hodgkin disease has been challenged in a recent report from the Pediatric Oncology Group [24]. This study concluded that after eight cycles of MOPP-ABVD, the addition of low-dose, total-nodal radiation did not improve the estimated event-free and overall survival. This finding, however, remains controversial and debated [25-28].

We recommend that leukemias and lymphomas in A-T patients be treated with cyclophosphamide whenever it is part of an SD chemotherapeutic schedule. Since the dose of cyclophosphamide varies from study to study, we suggest that mesna be used with cyclophosphamide until its use is shown to be of no benefit. Laboratory findings [22,23] and our clinical observations suggest that bleomycin be used with great caution in A-T patients, if at all. Since the chronic lung disease associated with A-T has an insidious onset and is progressive, we recommend that a careful respiratory history be taken, signs of fibrosis or chronic inflammation be sought on chest x-rays, and pulmonary function tests administered whenever cancer is diagnosed in an A-T patient. Unpublished clinical observations suggest that the progressive fibrosis and chronic inflammation may only be controlled by corticosteroids. Meticulous management of the A-T lung disease may lead to longer survival in patients who remit from their cancer with chemotherapy.

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