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Pilot study of modified LMB-based therapy for children with ataxia-telangiectasia and advanced stage high grade mature b-cell malignancies

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Abstract

Children with ataxia-telangiectasia (A-T) and cancer have a poorer prognosis due in part to increased treatment-related toxicity. We piloted a curative intent approach in five children with A-T who presented with advanced stage (III, n=2; IV, n=3) B-NHL (diffuse large B-cell lymphoma, n=4; Burkitt leukemia, n=1) using a modified LMB-based protocol. Two achieved sustained CCR (one, CCR at 6 years; one, pulmonary death after 3 years in CCR). Two died from toxicity during induction and 1 failed induction with progressive disease. Novel therapeutic approaches which overcome drug resistance and are less toxic are needed for children with A-T and B-NHL.

Keywords

ataxia-telangiectasia; non-Hodgkin lymphoma; Hodgkin lymphoma; children

Introduction

Ataxia-telangiectasia (A-T) is an autosomal recessive inherited disorder characterized by a diverse clinical phenotype including ataxia, dysarthria, progressive neuromotor degeneration, telangiectasias, elevated alpha-feto protein (AFP) levels, and a predisposition to developing cancer. [1] A-T is caused by mutations in the ATM gene; loss of ATM function results in the inability of cells from A-T patients to efficiently induce a number of cellular signaling pathways following DNA damage, such as DNA breakage caused by exposure to ionizing radiation. [1,2]

It has been estimated that approximately 10-30% of A-T patients will be diagnosed with a malignancy (primarily lymphoma and leukemia) at some point during their lifetime. [3] There is no consensus regarding the optimal strategy for treating children with A-T who develop a hematopoietic malignancy. Historically, many of these children have been treated with minimal or modified reduced-intensity therapy because of concerns regarding tolerance

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Disclosure

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of therapy. The BFM reported results of a reduced intensity regimen for 4 children with A-T and diffuse large B-cell lymphoma (DLBCL). [4] The three patients with limited stage disease were in continuous complete remission at the time of the manuscript; however, the one with advanced stage disease died from relapse. A subsequent BFM retrospective study indicated that 2 of 6 patients with advanced stage high grade mature B-cell lymphoma remained in CCR using a reduced intensity B-cell NHL regimen; another remained in CCR for 10 years until developing a second malignancy (DLBCL). Although all 6 patients received BFM-based therapy, the modifications were significant and not uniform. [5] A retrospective study of the treatment of lymphoid malignancies in patients with A-T by Sandoval et al, demonstrated that those treated with standard chemotherapeutic dosing had a significantly better median survival than those treated with reduced dose chemotherapy; however, the 5 B-NHL patients receiving standard dose therapy were all limited stage (I, n=5; II, n=1). [6] It is clear that children with A-T require a modification of certain components of intensive therapy and careful attention to supportive care. Here we report the results of the first prospective pilot study in the United States for children with A-T and advanced stage high grade B-cell lymphomas using modified LMB-based therapy.

Patients and Methods

Patients and workup

Children with a previously confirmed diagnosis of A-T, who were subsequently diagnosed with B-NHL, were eligible for our study (approved by our institutional review board and registered at ClinicalTrials.gov). All patients underwent a complete staging work-up that included computed tomography imaging of the neck, chest, abdomen and pelvis, functional radionuclide imaging (i.e., positron emission tomography scanning), and bone marrow and cerebrospinal fluid examination. [7]

Treatment

Treatment was based on successful contemporary approaches (e.g., SFOP LMB-89 regimen for B-cell lymphoma)[8] that were modified to take into account the unique toxicity profile which has been observed in A-T patients receiving chemotherapy (see Table 1). [9,10] Group C patients were treated according to the Group B arm (maximum methotrexate dosage given was 3 grams/m²). Those with CNS disease received additional intrathecal therapy.

Results

The histological subtypes, clinical features, treatment regimens, responses and outcomes for the 5 patients are summarized in Table 2 Additional details are described in the Supplemental Appendix.

Discussion

This small pilot study provides insights regarding the unique challenges encountered in the care of children with A-T and B-NHL. Poor outcome resulted from either treatment-associated toxicity or refractory disease. In spite of treatment modifications, increased

toxicity remained problematic for some. For example, the identification of adenoviral sepsis and subsequent liver failure, VOD and death would not be expected to occur in non-A-T patients receiving Group B therapy as per the LMB89 regimen.[8] This infection may reflect some degree of T-cell dysfunction. [11] Other examples of unusual toxicity included extra-pyramidal side effects following lorazepam, severe pulmonary leak associated with administration of low dose cytarabine infusion and late onset pulmonary failure. The etiology for the late onset pulmonary failure was not confirmed. Late onset pulmonary fibrosis has been reported in A-T patients who have received chemotherapy.[12] Alternatively, this may not have been a direct result of therapy. In this regard, interstitial lung disease has been reported in children with A-T not receiving chemotherapy. [13] Severe vincristine neuropathy was observed in one; additional data on this toxicity is needed.

The occurrence of induction failure in at least one of the 5 patients in this review suggests that malignancies occurring in children with A-T may be more resistant to standard therapy. This may be secondary to high risk biological characteristics in tumors that would otherwise be thought to be standard risk on the basis of histology alone. Another speculation is that refractory disease may be secondary to decreased chemotherapy-induced apoptotic signaling in the transformed cells, due to lack of ATM, resulting in inherent, biologically-resistant disease. [2,14] Other unusual biological features may also be present. In this regard, we previously reported that one of our patients with Burkitt leukemia presented with a novel t(3;8) translocation, not previously associated with Burkitt lymphoma;[15] this patient also presented with metabolic acidosis, a very uncommon high risk paraneoplastic feature in non-A-T patients with hematopoietic malignancies. [16] Clearly, further investigation into the biology of malignancies in children with A-T is needed.

The introduction of novel targeted therapeutic agents (monoclonal antibodies or small molecule inhibitors) into less intensive standard chemotherapeutic treatment regimens may help address both the challenges of treatment-associated toxicity and refractory disease. For example, R-CHOP [the combination of rituximab (anti-CD20) and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)][17] has been used successfully in a few A-T patients with diffuse large B-cell lymphoma. [18-20] Whether this approach will overcome the apparent drug resistance encountered in some A-T patients has

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Supplemental Appendix

Treatment outcomes and toxicity

Two patients achieved a sustained complete response (patient # 1 remains in CCR at 6 years from diagnosis and patient #5 remained in CCR until 3 years from diagnosis at which time he expired from pneumonitis/pulmonary failure of uncertain etiology). Two patients expired before response evaluation (# 2 and #3). One patient (#2) developed a clinical picture similar to that at diagnosis with abdominal distension and metabolic acidosis. No autopsy was performed, so recurrence versus sepsis could not be determined. Another patient (#3) developed typhilitis and adenoviral sepsis with veno-occlusive disease (VOD) and died. There was 1 induction failure (patient #4, refractory disease and expired secondary to multi-organ system failure as a complication of infection). The toxicity profile included those already described with LMB-based therapy; however two patients experienced severe infection and multi-organ system failure (e.g., seizures, cardiac failure, liver failure, renal failure) resulting in death in one (#3) and inability to receive further therapy in another [#4, refractory disease following induction therapy (i.e., COPADM #2)]. There were some additional toxicities that we considered to be uncommon in the context of the therapy delivered. These included extra-pyramidal side effects following lorazepam in two patients, severe vincristine peripheral sensory neuropathy (i.e., severe bilateral lower extremity pain) in one patient, and severe pulmonary leak during low dose continuous cytarabine infusion (Group B CYM therapy) in one patient[8].

yet to be determined. Moreover, the toxicity profile of rituximab in A-T patients has not been established. Additional data is needed for this approach in A-T patients with DLBCL.

In conclusion, refinement in the treatment approach to children with A-T and advanced stage B-NHL is needed. Those with Burkitt lymphoma may need additional modifications to LMB-based therapy. The incorporation of Rituximab (R-CHOP) for CD-20+ DLBCL, is worthy of investigation. Multicenter trials which investigate both innovative treatment approaches and cancer biology in A-T patients with B-NHL should result in improved outcomes.

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Table 1
Suggested Treatment Modifications and Supportive Care Recommendations for A-T Patients Receiving Cancer Therapy.

Medical vulnerability	Treatment Modification	Supportive care
1) Increased sensitivity to ionizing radiation and radionuclides	Avoid/limit dose of radiation and radionuclides (e.g., bleomycin)	- Use diagnostic x-rays as needed for state of the art medical care. - Consider use of alternate imaging modalities (e.g. ultrasonography, magnetic resonance imaging).
2) Mucosal damage/repair leading to telangiectasias and late onset bleeding:		
a) Late onset hemorrhagic cystitis from cyclophosphamide and ifosfamide	Administer Mesna with all doses of these agents	Provide aggressive hydration with all doses of these agents
b) Late onset GI bleeding post Mucositis		- Optimize methotrexate clearance. - Avoid concurrent nephrotoxic agent - Prophylactic use of H2 receptor agonist or proton pump inhibitor
3) Increased risk of life threatening infections while receiving chemotherapy		- Intervene early with broad spectrum antibiotics. - Administer IVIG in some cases
4) Ambulation compromised by chemotherapy induced peripheral neuropathy	- Limit use of weekly vinca alkaloids. - Consider substitution with less neurotoxic vinca alkaloid, vinblastine. - Baseline neuroimaging - Baseline neurology consultation	
5) Increased sensitivity to topoisomerase II inhibitors	Reduce (25%) dosage for these agents (e.g., daunorubicin, etoposide).	
6) Poor weight gain while on therapy		- Order nutrition consults. - Consider total parenteral nutrition with inadequate oral intake. - Place central catheter (double lumen). - Baseline chewing and swallowing evaluation to determine need for G-tube placement

Table 2

Clinical Characteristics of Children with A-T Who Developed Cancer

Patient No	Age (yrs)	Diagnosis	Disease sites	Stage	Treatment	Response	Outcome
1	8	DLBCL	Waldeyers ring; kidney; pelvis	III	LMB-89	CR	Alive in CCR 5 years
2	11	B-ALL	Bone marrow; CNS+	IV	LMB-89	Inevaluable	Expired secondary to relapse versus sepsis
3	9	DLBCL	Multiple nodes; CNS+	IV	LMB-89	Inevaluable	Expired secondary to enterococcal bacteremia; adenoviral sepsis; multi-organ system failure and VOD
4	6	DLBCL	Multiple nodes; liver; spleen, BM+	IV	LMB-89	Induction failure (progressive disease after COPADM #2)	Expired secondary to multi-organ system failure and induction failure
5	19	DLBCL	Waldeyers ring; mediastinum, multiple nodes	III	LMB-89	CR	Expired 3 years from diagnosis from pneumonitis

Histological subtypes included DLBCL (diffuse large B-cell lymphoma) and B-ALL (Burkitt Leukemia). Distant sites of disease included BM (bone marrow) and CNS (central nervous system). Treatment was derived from LMB-89 (French Society of Pediatric Oncology treatment regimen for mature B-cell malignancies). Responses included CR (complete remission) and CCR (continuous complete remission). Toxicity included VOD (veno-occlusive disease).