Response but severe toxicity with low dose decitabine in a Werner’s syndrome patient with acute myeloid leukemia and t(9;19)(p13;p13)

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Abstract

Werner’s syndrome is a rare autosomal recessive premature aging syndrome caused by mutations in the Werner RecQ helicase. Patients typically die in their 5th decade from cardiovascular disease or cancer. There are few reports of the treatment of malignancies in these patients. We previously reported a patient with Werner’s syndrome who expired from multi-organ failure after treatment of AML with intensive chemotherapy. We currently report a patient with Werner’s syndrome and AML who was treated with decitabine, a low intensity regimen commonly used to treat elderly patients. This patient also developed severe toxicity, but recovered and obtained a complete remission. Unfortunately the patient’s disease progressed 5 months later and he then expired.

Introduction

Werner’s syndrome is a rare autosomal recessive premature aging syndrome caused by mutations in the Werner RecQ helicase, an enzyme involved in repair of double strand DNA breaks and telomere replication [1,2]. When mutated, WRN causes sporadic loss of telomeres, increased DNA damage, genomic instability and premature senescence [3]. The clinical symptoms of Werner’s syndrome begin in the early teens with loss of the growth spurt, followed by more progressive signs and symptoms in the 20’s and 30’s including graying of the hair, hoarseness, scleroderma-like skin changes, bilateral cataracts, type 2 diabetes, hypogonadism, skin ulcers and osteoporosis [1]. Patients typically die in their 5th decade from cardiovascular disease or cancer.

Case Report

Due to the rarity of this disease, there are very few reports of the treatment of malignancies in patients with Werner’s syndrome. We previously reported a patient Werner’s syndrome who was treated with high dose cytarabine, etoposide and mitoxantrone for newly diagnosed AML [4]. The patient expired from multi-organ failure three weeks after initiation of therapy. We hypothesized that this severe toxicity was secondary to the increased sensitivity of the patient’s normal cells to chemotherapy due to defective DNA repair from Werner’s syndrome. We currently report a second patient with Werner’s syndrome and AML. Based on our prior experience we treated the patient with decitabine, a low intensity regimen commonly used to treat elderly patients. The patient again developed severe toxicity, but this time he recovered and obtained a complete remission. Unfortunately the patient’s disease progressed 5 months later and he then expired.

The patient was 42-year-old man who presented when a low white blood count was noted on blood work performed prior to surgery for a leg ulcer. The patient had a history of type II diabetes since his early 20’s. He underwent bilateral cataract surgery shortly after that. The patient developed coronary artery disease requiring CABG while in his 30’s. He also had a history of peripheral vascular disease including carotid stenosis, hypercholesterolemia, and hypothyroidism. Recently he had developed a non-healing ulcer on his left heel and was scheduled for surgery. The patient’s medications upon admission were metoprolol, clopidogrel, aspirin, levothyroxine, rosuvastatin, and insulin. Several of the patient’s maternal relatives had cardiovascular disease, but later in life. His father had an unknown type of cancer. No other family members had manifestations of Werner’s syndrome and there was no known consanguinity. The patient was of Hispanic (Puerto Rican) ethnicity.

On physical examination the patient appeared chronically ill and had a distinctive habitus. He was 5 feet tall (several inches shorter than any of his relatives) and weighed 93 pounds. He had a high-pitched, hoarse voice and a beak-like nose. His hair was thin and blonde; however he dyed his hair which had been grey for years. His extremities were particularly thin. His skin was taut with a scleroderma-like appearance. There was a healed ulcer over the right elbow and an open ulcer on the left foot. His feet were flat with callouses on the heels. There were artificial lenses in both eyes. He also had a history of peripheral vascular disease including carotid stenosis, hypercholesterolemia, and hypothyroidism. Recently he had developed a non-healing ulcer on his left heel and was scheduled for surgery. The patient’s medications upon admission were metoprolol, clopidogrel, aspirin, levothyroxine, rosuvastatin, and insulin. Several of the patient’s maternal relatives had cardiovascular disease, but later in life. His father had an unknown type of cancer. No other family members had manifestations of Werner’s syndrome and there was no known consanguinity. The patient was of Hispanic (Puerto Rican) ethnicity.

Laboratories showed a white blood count (WBC) of 1900/mm³, with 15% neutrophils, 82% lymphocytes, and 3% monocytes. The...
hemoglobin was 9.7 gm/dl and the platelet count was 191,000/mm³. An echocardiogram demonstrated moderate aortic stenosis. Plain films of the foot demonstrated osteosclerosis and soft tissue calcifications (Figure 1). Osteomyelitis was noted on an MRI of the left foot.

The bone marrow aspirate was hemodilute with 16% blasts. The core biopsy was hypercellular with a diffuse increase in reticulin fibrosis. Blasts were estimated at 25% to 30%. On flow cytometry the blasts demonstrated CD13 (subset), CD33 (dim), CD34, CD117, CD11c (dim), HLA-DR, CD64 (dim), CD38, CD71, CD9 (dim), and were negative for CD61, CD56, TdT, and B and T lymphoid markers. Cytogenetics showed 46,XY, t(9;19)(p13;p13)[1]/44,idem.-3,del(5)(q22q33),-7,add(11)(q23),del(17)(p12) [7]/46,XY[12]. FLT3 and NPM were not mutated.

We planned to treat the patient with decitabine 20 mg/m² daily for 5 days, a low intensity chemotherapy regimen that is commonly used in elderly AML patients. However after the third dose the patient’s course became very similar to that of our previous patient. He developed high fevers, diffuse pulmonary infiltrates, and hypotension requiring vasopressors. Further chemotherapy was withheld. He had progressive respiratory failure and required intubation on day 4 (Figure 2). Bronchoalveolar lavage demonstrated diffuse pulmonary hemorrhage. All cultures showed no growth of organisms. The patient was treated empirically with steroids and broad spectrum antibiotics. Although the patient was critically ill, he gradually improved and was extubated after 18 days of intubation. His renal function which had deteriorated transiently recovered without dialysis. On day 30 his WBC was 5000/mm³ with 60% neutrophils, 29% lymphocytes, 6% monocytes, 1% basophils, 3% metamyelocytes, and 1% myelocytes. The hemoglobin was 9.0 gm/dl and the platelet count was 208,000/mm³. Bone marrow done on day 27 showed a normocellular marrow with trilineage hematopoiesis, mild dyserythropoiesis, dysmegakaryopoiesis and 1% blasts. Cytogenetics demonstrated 46,XY, t(9;19)(p13;p13.3)[7]/44,idem.-3,del(5)(p22q33),-7,add(11)(q23),del(17)(p12) [13]/46,XY,idem.del(5)(q22q33)[1]/46,XY[9]. Molecular studies performed at the University of Washington School of Medicine (Drs. Junko Oshima and George Martin) through the International Registry of Werner syndrome demonstrated a homozygous mutation c.1105C>T (p.Arg369Stp) in exon 9. This is the most common WRN mutation among Caucasian patients, seen in 20% of cases [5]. Western analysis showed no detectable WRN protein.
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