

# Total Body Irradiation in a Patient with Fragile X Syndrome for Acute Lymphoblastic Leukemia in Preparation for Stem Cell Transplantation: A Case Report and Literature Review

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Fragile X syndrome (FXS) is a congenital disorder caused by expansion of CGG trinucleotide repeat at the 5' end of the fragile X mental retardation gene 1 (*FMR1*) on the X chromosome that leads to chromosomal instability and diminished serum levels of fragile X mental retardation protein (FMRP). Afflicted individuals often have elongated features, marfanoid habitus, macroorchidism and intellectual impairment. Evolving literature suggests the condition may actually protect from malignancy while chromosomal instability would presumably elevate the risk. Increased sensitivity to ionizing radiation should also be predicted by unstable sites within the DNA. Interestingly, in this report, we detail a patient with FXS diagnosed with acute lymphoblastic leukemia treated with induction followed by subsequent cycles of hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) with a complete response who then was recommended to undergo peripheral stem cell transplantation. The patient underwent total body irradiation (TBI) as a component of his conditioning regimen and despite the concern of his clinicians, developed minimal acute toxicity and successful engraftment. The pertinent literature regarding irradiation of patients with FXS is also reviewed. © 2015 Wiley Periodicals, Inc.

**Key words:** Total body irradiation; fragile X; stem cell transplant; acute toxicity

## INTRODUCTION

Fragile X syndrome (FXS) is caused by a mutation in the Fragile X Mental Retardation 1 (*FMR1*) gene. It is the most common inherited cause of intellectual disability, with a prevalence of approximately 1:4000 males, twice that of females with a carrier rate roughly three times higher [Rousseau et al., 1995; Turner et al., 1996; de Vries et al., 1997]. The most common mutation is expansion of CGG trinucleotide repeats in the 5' region of the

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*FMR1* gene triggering hypermethylation, leading to subsequent transcription silencing of the fragile X mental retardation protein (FMRP), with variable levels associated with phenotypic heterogeneity [Lessard et al., 2012]. Patients with fragile X syndrome may have enlarged chins and ears, high arched palates, macroorchidism, hyper-flexibility, intellectual disability and features of autism spectrum disorder. Women with FXS often display a milder phenotype due to heterogeneous expression of the fragile X chromosome.

Total body irradiation (TBI) is used in conditioning for stem cell transplantation to prevent rejection, clear space within the marrow and eliminate malignant cells in sanctuary sites. Acute toxicities include headache, nausea, vomiting, diarrhea, fatigue, skin erythema and painful swelling of the parotid glands (parotitis). Sub-acutely, alopecia, mucositis and xerostomia have been reported. Chronic toxicities include pneumonitis (peak 2–3 months), hepatic sinusoidal obstructive syndrome, sterility, endocrine disturbances,

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pericarditis, cataract formation and secondary malignancies [Halperin et al., 2008].

The following case describes a patient with FXS suffering from acute lymphoblastic leukemia (ALL) that underwent TBI with etoposide conditioning for hematopoietic stem cell transplant and suffered limited toxicity with successful engraftment.

## CLINICAL REPORT

The patient is a 31-year-old male with FXS diagnosed with Philadelphia chromosome negative B-cell acute lymphoblastic leukemia after workup for anemia. Initial bone marrow biopsy showed 91% blasts, phenotyped as precursor B-cells with a complex karyotype. The patient underwent induction followed by five cycles of hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone). Subsequent bone marrow biopsy showed hypocellular marrow with mature lineage and no evidence of blasts. To gain the survival advantage from peripheral stem cell transplantation after a good response to initial therapy, a decision was made to proceed with transplant [Vose et al., 1993].

Radiation Oncology was consulted for stem cell conditioning using TBI. At consultation, the patient complained of fatigue, alopecia and weight loss. He was approximately six feet tall with a marfanoid habitus and history of mitral valve insufficiency. Scrotum measured 3.5 cm in depth consistent with macroorchidism. The FXS diagnosis was made as a child by peripheral lymphocyte cytogenetics; he was never tested for serum FMRP. He displayed moderate intellectual impairment which may suggest some level of mosaicism [Pretto et al., 2014], but was able to function independently in his activities of daily living.

TBI was accomplished using an AP-PA beam arrangement in twice daily fractions of 165 cGy at a dose rate of 15cGy/minute for 8 total fractions. The total dose was 1320 cGy over days -7 to -4 followed by a single 400 cGy boost to the testes using *en face* electrons. On day -3, 60 mg/kg etoposide was administered. A successful 10/10 matched, unrelated donor allogeneic peripheral stem cell infusion was then performed. Post-transplant, the patient had an isolated episode of neutropenic fever and mild diarrhea managed with Immodium. He did develop WHO grade I mucositis by day +4 that progressed to WHO grade III by day +6 and resolved by day +12 after management with Mary's magic mouthwash and IV opioids. Notably, the patient had several episodes of mucositis throughout his prior chemotherapy courses. He was placed on tacrolimus and sirolimus for graft-versus-host disease prophylaxis with acyclovir, fluconazole, and sulfamethoxazole/trimethoprim prophylactic antibiotics. The patient developed mild scrotal erythema without edema or desquamation that resolved by day +17. Following discharge, the patient noted only hair loss and resolving fatigue, denying shortness of breath, cough, chest discomfort or parotitis.

No signs or symptoms of pneumonitis, pericarditis, parotitis, liver dysfunction, cognitive decline, xerostomia or hypothyroidism were evident at six month follow-up. Physical exam revealed resolving alopecia and laboratory evaluation confirmed no evidence of organ dysfunction. Immunosuppressive agents were within therapeutic range with no evidence of graft-versus-host disease. His day +100 bone marrow biopsy revealed mildly hypocellular bone marrow with maturing trilineage hematopoiesis

completely of donor origin, consistent with successful engraftment and continued complete response.

## DISCUSSION

This patient's case is unique in that it describes TBI in the setting of FXS. Patients with FXS were originally postulated to have increased susceptibility to malignancy due to fragile DNA sites susceptible to chromosomal rearrangement and subsequent tumor initiation or promotion [Durkin and Glover, 2007]. A 1990 study found an increased frequency of bleomycin-induced chromatid breaks in lymphocytes cultured from a patient with FXS compared to controls [Li and Lin, 1990]. A 2005 publication described carboplatin, docetaxel, and trastuzumab precipitating tremor and ataxia in a woman with FXS pre-mutation [O'Dwyer et al., 2005].

Despite this, several studies have shown a normal to decreased malignancy rate in patients with FXS. Using information from the Danish Cytogenetic and Cancer Registries, a study of 223 patients with FXS found a negative correlation between FXS and malignancy rate, indicating a possible protective effect [Schultz-Pedersen et al., 2001]. An Australian study reviewed 348 males and 433 females with FXS and found no increase in cancer related mortality [Partington et al., 1992]. In these FXS studies, malignancy risk can be seen as a surrogate for susceptibility to RT side effects, as unstable DNA sites should predispose to both. Notably, recent molecular work by Bagni and colleagues suggests that FMRP stabilizes mRNAs associated with murine models of breast cancer invasion and lung metastasis [Luca et al., 2013].

In a recent report by Paulino and colleagues, 42 cases of neoplasia in patients with FXS were reviewed and three describe the use of RT [Farach et al., 2013]. Review of each primary source reveals no commentary on RT toxicity [Ferrari et al., 2000; Rodewald et al., 2005; Garre et al., 2009]. The authors describe two new cases. The first is of a 10-year-old that underwent RT for a brainstem glioma resulting only in mild in-field alopecia. The second reports on a 23-year-old male who received adjuvant radiotherapy for a juvenile nasopharyngeal angiofibroma. The patient suffered mild self-limited oral erythema and xerostomia following RT and by 8 months displayed no toxicities. Initial concerns of increased radiation sensitivity in FXS are seemingly refuted by these reports showing minimal acute toxicity with no chronic toxicities yet appreciated.

No research exists on TBI in patients with FXS. Down syndrome (trisomy 21) remains the chromosomal abnormality where TBI has been most thoroughly described. A 1986 series suggested increased radiosensitivity in three of four children with adverse reactions including severe desquamation, mucositis, pneumonitis and prolonged radiation enteritis [Rubin et al., 1986]. A 1996 report described only mild mucositis in two patients with Down syndrome treated with a regimen of cytosine arabinoside and fractionated TBI [Conter et al., 1996]. Another study investigated toxicities in 27 patients with Down syndrome who received chemotherapy and TBI conditioning, concluding that there were higher rates of life-threatening and fatal toxicity, while also cautioning that these patients were able to complete standard conditioning with manageable, acceptable rates of toxicity [Rubin et al., 1996]. Additionally, an increased risk of early pneumonitis in

Down syndrome patients treated with chemotherapy and TBI has been reported [Rubin et al., 1986; Rubin et al., 1996].

Per the aforementioned studies, patients with FXS suffer no increased acute RT toxicity and may actually show increased resistance to the adverse effects of radiation. Our case reports on minimal acute toxicities of TBI in a patient with FXS. In contrast to studies of Down syndrome, we report limited TBI toxicity of mucositis, diarrhea and fatigue in the acute setting with minimal skin erythema and alopecia subacutely. No pulmonary, hepatic, renal or endocrine dysfunction has been appreciated. Based on the literature review and our case, it appears that TBI, and RT in general, is acutely safe in patients with FXS. Further prospective studies are needed to confirm these findings and investigate the long-term toxicities of TBI in patients with FXS.

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