Original Study

Use and Effectiveness of Gonadotropin-Releasing Hormone Agonists for Prophylactic Menstrual Suppression in Postmenarchal Women Who Undergo Hematopoietic Cell Transplantation

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A B S T R A C T

Study Objective: To describe the rates of use and effectiveness of gonadotropin-releasing hormone (GnRH) agonists and other forms of hormonal menstrual suppression in prevention of vaginal bleeding among young women who underwent hematopoietic stem cell transplantation (HCT).
Design: Retrospective descriptive study.
Setting: University-based pediatric HCT practice.
Participants: Fifty-five postmenarchal women who underwent HCT between 2004 and 2011.
Interventions: Administration of GnRH agonists or other forms of hormonal menstrual suppression.
Main Outcome Measures: Rates of use of GnRH agonists and other forms of hormonal menstrual suppression, and rates and descriptions of vaginal bleeding.
Results: Forty-six of the 55 patients had experienced regular or irregular vaginal bleeding before HCT and were considered to be at risk for thrombocytopenia-associated menorrhagia. Forty of the 46 (87%) received hormonal menstrual suppression. Thirty-three patients were treated with a GnRH agonist, 4 with combined hormonal contraceptive pills, 1 with a combined hormonal contraceptive patch, 1 with depot medroxyprogesterone, and 1 with oral norethindrone. Twenty-nine of the 33 patients (88%) who received a GnRH agonist had complete amenorrhea during HCT and 4 of 33 (12%) experienced some degree of vaginal bleeding.
Conclusion: GnRH agonists appear effective in prevention of vaginal bleeding complications in most postmenarchal women who underwent HCT. Some patients who might benefit do not receive a GnRH agonist and multiple barriers exist in identification and treatment of them.
Key Words: Gonadotropin-releasing hormone, Menorrhagia, Hematopoietic stem cell transplantation

Introduction

Patients who undergo myeloablative hematopoietic stem cell transplantation (HCT) receive preparative conditioning that consists of high doses of chemotherapy with or without total body irradiation. For pubertal women, vaginal bleeding occurs commonly during HCT, and is exacerbated by thrombocytopenia or other coagulopathies associated with HCT.[1] Menorrhagia, particularly before platelet engraftment, can be a significant problem. It often requires transfusion of red cells and/or platelets, which increases patient risk of alloimmunization and infection,[2,3] or medical therapies such as estrogen, which can cause hepatic or other toxicities. Gonadotropin-releasing hormone (GnRH) agonists, such as leuprolide acetate (Lupron; AbbVie Inc, North Chicago, IL), are commonly used in postmenarchal females before HCT to induce amenorrhea as a means to prevent thrombocytopenia-associated menorrhagia. Published case series report rates of amenorrhea associated with GnRH agonist administration of 90% and higher with no reported adverse events.[4,5] There is a paucity of data on the approach to menstrual suppression in young postmenarchal women who undergo HCT. Herein we describe approaches to menstrual suppression with a focus on the rate of GnRH agonist use and its efficacy in prevention of vaginal bleeding during the acute HCT period.

Materials and Methods

We performed a retrospective descriptive study of female patients at Boston Children's Hospital and Dana-Farber Cancer Institute who underwent HCT for any indication between January 1, 2004 and June 1, 2011. Our institutional database was queried for patients aged 8 years or older to capture all patients who could have experienced normal menstrual periods or irregular vaginal bleeding and

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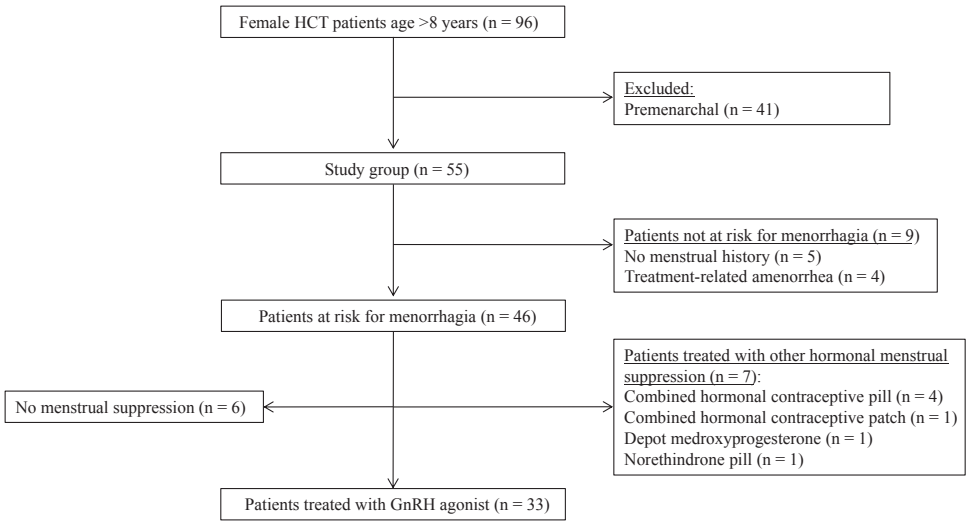

Fig. 1. Flowchart of study group inclusion and exclusion. GnRH, gonadotropin-releasing hormone; HCT, hematopoietic stem cell transplantation.

to exclude all patients who could have experienced precocious puberty. Ninety-six patients were initially identified; 41 were premenarchal and were excluded from further analysis (Fig. 1). The median age of the 55 patients in the study group was 16 years (range, 9-33 years; Table 1). All patients received conditioning regimens that included alkylating chemotherapy with or without the addition of total body irradiation (13.2-14.0 Gy). All patients who received prophylactic GnRH agonist treatment for menstrual suppression were analyzed for the effectiveness of GnRH agonists in prevention of vaginal bleeding during transplantation. Patients who did not receive prophylactic menstrual suppression with a GnRH agonist but received a GnRH agonist for menorrhagia during HCT were not assessed. Any vaginal bleeding during HCT, whether or not it required treatment, was considered failure of menstrual suppression and details of the bleeding were recorded. All data were gathered from the electronic medical record system and no subjects were contacted for additional information. Study data were collected and managed using Research Electronic Data Capture tools hosted at Partners Healthcare.[6] The use and effectiveness of GnRH agonists in prevention of vaginal bleeding complications were evaluated with descriptive statistics and the analysis of variance test. The study was reviewed and approved by the institutional review board of the Dana-Farber Cancer Institute.

Table 1
Patient, Disease, and Treatment Characteristics

Characteristic	Value
Age at time of transplant	16 (9-33)
Diagnosis	
Hematologic malignancy	43
Solid tumor	2
Nonmalignant disease	10
Conditioning regimen	
Chemotherapy alone	25
Chemotherapy and TBI	30
Transplant type	
Autologous	16
Unrelated donor	25
Related donor	14
Source	
PBSC	19
Bone marrow	31
Cord	5

TBI, total body irradiation; PBSC, peripheral blood stem cells
Data are presented as n or median (range).

Results

Of the 55 patients, 46 had regular or irregular vaginal bleeding before HCT and were considered to be at risk for thrombocytopenia-associated menorrhagia and eligible for prophylactic hormonal menstrual suppression. Four patients had treatment-related amenorrhea and 5 patients had no recorded menstrual history. Of the 46 at-risk patients, 40 (87%) received hormonal menstrual suppression, 33 (72%) with a GnRH agonist. Thirty-two patients received leuprolide acetate intramuscular injection. Dosing information was available for 21 patients; 2 patients received 3.75 mg, 1 patient received 7.5 mg, 5 received 11.25 mg, and 13 received 22.5 mg. One patient received goserelin acetate (Zoladex; AstraZeneca Pharmaceuticals LP, London, United Kingdom; dose and route not available). Among the 31 patients for whom timing of GnRH agonist therapy was documented, it was initiated a median of 46 days before the start of conditioning (range, −9 to 183 days). It was administered within 14 days of HCT to 9 patients and after conditioning began in 1 patient. Of the patients who received a GnRH agonist, amenorrhea during the HCT admission was successfully induced in 29 of 33 (88%).

Four of the 33 patients (12%) treated with a GnRH agonist, 2 of 7 (29%) treated with other hormonal prophylaxis, and 4 of 6 (67%) who did not receive menstrual suppression experienced vaginal bleeding ($P < .01$; Fig. 2). Descriptions of bleeding events among each group are provided.

Patients with Bleeding Who Had Prophylaxis with a GNRH Agonist

Patient 1 had a history of severe menorrhagia more than 2 months earlier during her hospitalization for induction