Published in final edited form as:
Obstet Gynecol. 2013 February ; 121(2 0 2 0 1): 424–427.

Management of Uterine Bleeding During Hematopoietic Stem Cell Transplantation

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Abstract

BACKGROUND—Hematopoietic stem cell transplant is an effective treatment strategy for a variety of hematologic disorders, but patients are at risk for dysfunctional coagulation and abnormal bleeding. Gynecologists are often consulted before transplant for management of abnormal uterine bleeding, which may be particularly challenging in this context.

CASE—A premenopausal woman with MonoMAC (a rare adult-onset immunodeficiency syndrome characterized by monocytopenia and *Mycobacterium avium* complex infections resulting from mutations in *GATA2*, a crucial gene in early hematopoiesis) presented with pancytopenia, evolving leukemia, and recent strokes, necessitating anticoagulation. During preparation for hematopoietic stem cell transplant, she experienced prolonged menorrhagia requiring transfusions. Surgical therapy was contraindicated, and medical management was successful only when combined with balloon tamponade.

CONCLUSION—Balloon tamponade may be a potentially life-saving adjunct to medical therapy for control of uterine hemorrhage before hematopoietic stem cell transplant.

Regardless of the indication for hematopoietic stem cell (HSC) transplant, the management of patients in the peritransplant period is complex and benefits from an interdisciplinary approach. Gynecologists are often consulted before transplant for contraception counseling and also for menses suppression because underlying disease-related cytopenia, coupled with thrombocytopenia occurring with conditioning chemotherapy, predisposes patients to potentially life-threatening menorrhagia.[1] The management of uterine bleeding in the context of HSC transplant can be difficult because typical methods of menses suppression may be contraindicated and others may not be successful.

"MonoMAC" is a recently described adult-onset immunodeficiency syndrome characterized by monocytopenia and *Mycobacterium avium* complex infections resulting from mutations in *GATA2*, a crucial gene in-early hematopoiesis.[2,3] In addition to peripheral monocytopenia, patients with MonoMAC have profound B and NK lymphocytopenia. They

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Financial Disclosure
The authors did not report any potential conflicts of interest.

are susceptible not only to disseminated nontuberculous mycobacterial infections, but also to viral infections, specifically severe extensive human papillomavirus disease, and disseminated fungal infections. Development of myelodysplasia and leukemic transformation are common. HSC transplant has been reported as an effective treatment strategy that reverses both the hematologic and immunologic manifestations of MonoMAC.[4]

The peritransplant management of patients with MonoMAC requiring menses suppression may pose additional challenges. First, individuals with MonoMAC appear to have an inherent prothrombotic tendency, which limits the use of estrogenic agents (Sanchez LA, Cuellar-Rodriguez J, Zerbe CS, Hsu AP, Freeman AF, Hickstein DD, et al. Thrombotic complications in GATA2 deficiency, Primary Immune Deficiency Diseases North American Conference, 2012). Second, patients with MonoMAC with leukemic transformation have an urgent need for transplantation but may have thrombocytopenia, which is exacerbated by induction chemotherapy before transplant. The short timeline to transplantation limits the options for surgical management of uterine bleeding. We report a case of prolonged menorrhagia during the peritransplant period in a patient with MonoMAC and describe how to approach abnormal uterine bleeding in female transplant patients.

CASE

A 38-year-old woman with MonoMAC was under care at the National Institutes of Health Clinical Center, preparing to undergo HSC transplant. The plan was to begin chemotherapy immediately and expedite the transplant because a recent bone marrow biopsy showed a markedly hyper-cellular bone marrow and evidence of evolving leukemia with 5% blasts. The patient was pancytopenic with a hemoglobin as low as 7.4 g/dL and platelets as low as 36,000/microliter. Independent of menstrual bleeding, she was receiving both packed red blood cells (approximately 2 units weekly) and platelets (approximately 4–6 units every 4 days) to maintain her counts. In this setting, the gynecology consult service was consulted for menses suppression before transplant. Although previously the patient had regular menses, with no history of menorrhagia, the referring team requested a strategy to limit menstrual bleeding because chemotherapy in preparation for transplantation would further compromise her blood counts.

Related to her diagnosis of MonoMAC, the patient had signs of a then-unknown immunodeficiency beginning at age 12 years. Her more recent medical history was notable for extensive vulvar and perirectal human papillomavirus-associated high-grade dysplasia, which began in her 20s and was treated with numerous surgical procedures and skin grafting. She was found to have atypical mycobacterial infections in her early 30s. To treat and control her various other infections, her antibiotic therapy included azithromycin, levofloxacin, rifampin, vancomycin, and acyclovir. She also had a history of recurrent deep venous thrombosis and, recently, multiple new strokes. The first stroke, 3 weeks before gynecology consult, involved the left middle cerebral artery and presented with aphasia and right upper extremity paralysis that resolved after administration of tissue plasminogen activator. The second stroke, on the day of consultation, presented with visual changes, which slowly resolved with anticoagulation. She was treated for culture-negative endocarditis after transesophageal echocardiogram revealed thickening of the mitral and aortic valve leaflets. Thorough hematologic evaluation for the factor V Leiden mutation, the prothrombin gene mutation, and other less common causes of an inherited thrombophilia was negative. A follow-up brain magnetic resonance imaging, however, revealed a pattern suggesting new embolic phenomena with resultant subclinical infarcts. In the absence of another etiology, the clinical picture suggested a hypercoagulable state related to MonoMAC, and she therefore was maintained on enoxaparin indefinitely.

The patient was initially started on 3.75 mg leuprolide intramuscularly for menses suppression, which was administered in the late luteal phase of her menstrual cycle. Unfortunately, menses began as expected 2 days after the first treatment. She began having menorrhagia such that during 10 days of bleeding, the patient required approximately 2 units of packed red blood cells every 4 days and 4–6 units of platelets every 3 days. An anti-Xa level of 1.5 was higher than the goal of 1.0, but she continued to have bleeding after her enoxaparin dose was adjusted. Recent pelvic magnetic resonance imaging revealed a 5-cm intramural fibroid and a 1-cm submucosal leiomyoma, the latter being more likely to contribute to the current menorrhagia.

Because she was scheduled to begin induction chemotherapy in 5 days, the transplant team requested an immediate intervention to stop the patient's bleeding. Three doses of 25 mg intravenous estrogen were administered 6 hours apart. After the second dose of estrogen, bleeding worsened such that she was soaking through one pad every hour. Hemoglobin was 7.6 g/dL and platelet count was 44,000/microliter.

In the context of failing to respond to medical therapy, a 16-French Foley catheter with a 30-mL balloon was placed, using a sterile technique, into the uterus to balloon tamponade the endometrium. Placement above the cervix was confirmed with transabdominal ultrasonography, after which 5 mL of saline was instilled into the balloon. With the balloon catheter in place, the bleeding decreased. The Foley catheter remained in the uterus for 3 days. During this time, the patient was started on 10 mg medroxyprogesterone daily. She had minimal bleeding but as hemoglobin levels reached a nadir of 6.5 g/dL, she received 2 units of packed red blood cells.

The patient had minimal bleeding while she was maintained on 10 mg medroxyprogesterone daily and 3.75 mg leuprolide intramuscularly every 21 days. Three weeks after induction chemotherapy given as part of transplantation, platelets dropped to 13,000/microliter. Vaginal bleeding worsened, and 0.625 mg daily of conjugated estrogen was added. Because the vaginal bleeding would occur 17 days after the leuprolide injection, the frequency of leuprolide dosing was also adjusted to every 17 days to prevent breakthrough bleeding. Medroxyprogesterone was tapered to 5 mg daily. On this regimen of leuprolide as well as dual hormone therapy (medroxyprogesterone and estrogen), the patient had minimal bleeding and safely made it through stem cell transplant approximately 2.5 months after initial consult. By 10 months post-HSC transplant, she was doing extremely well with complete engraftment and minimal graft-versus-host disease and thus was not anticipated to require additional stem cell transplants.

COMMENT

We present a case in which medical therapies to treat menorrhagia requiring transfusions in the prestem cell transplant preparation were limited and failed initially until they were combined with balloon tamponade. Patients in the peristem cell transplant period are at high risk for abnormal uterine bleeding, but currently no standardized approach exists for the prevention and management of menorrhagia in this population.

Menses suppression before beginning conditioning chemotherapy may be a reasonable strategy for patients undergoing stem cell transplant.[5] Studies have shown that using a gonadotropin-releasing hormone (GnRH) agonist (leuprolide) is a safe and effective method of prophylactic menses suppression in patients undergoing stem cell transplant with complete prevention of uterine bleeding during the period of profound thrombocytopenia in 73–97%.[6] As an additional benefit, GnRH agonists have a potential role in ovarian preservation. One must carefully consider the timing of administration of a GnRH agonist in

relation to the expected thrombocytopenia, although because these agents initially cause a brief flare in the luteinizing hormone and follicle-stimulating hormone levels. This surge may trigger ovulation and, as occurred in our case, menstruation before the pituitary desensitization and hormone suppression that occurs a few weeks later. Administration of a GnRH agonist during the luteal phase may reduce the likelihood of a surge in gonadotropins and limit bleeding, but this timing is not always possible. Another consideration is the frequency of GnRH agonist dosing in this population. Although standard dosing of leuprolide intramuscularly is every 28 days, our patient ultimately required dosing every 17 days. We often shorten the redosing interval at our center for patients with early bleeding because complex polypharmacy regimens presumably increase the metabolism of leuprolide.

Unfortunately, because GnRH agonists are not 100% effective and because many patients cannot afford a delay in chemotherapy, therapeutic amenorrhea cannot always be achieved before transplantation. In these cases, health care practitioners must then be able to treat the menorrhagia that often occurs in the setting of profound thrombocytopenia resulting from chemotherapy. A general approach to abnormal uterine bleeding involves consideration of both medical and surgical management strategies in addition to supporting patients with blood product transfusions.

Regarding medical management, hormonal therapy is typically first line for the management of acute menorrhagia. One possible option is to use high-dose oral contraceptive pills. However, the use of oral contraceptive pills may be limited as a result of inability to tolerate oral formulations, higher rates of hepatotoxicity, or, like in this case, prothrombotic tendencies related to the patient's underlying disease. An alternative, and perhaps more effective, option is intravenous estrogen, 25 mg intravenously every 6 hours for 24 hours. Like with oral contraceptive pills, this approach carries a risk of liver toxicity and venous thrombosis. However, there may be cases, like ours, in which bleeding is so severe and potentially life-threatening such that risk–benefit analysis favors the use of a short course of estrogen treatment despite the usual contraindications to hormonal therapy. Of note, concomitant use of anticoagulation might lessen the risks of hormonal therapies in patients with a history of venous thromboembolism or stroke.

As demonstrated in this case, there are patients for whom medical therapies are insufficient or contraindicated. In general, when various medical therapies fail to control uterine bleeding, surgical intervention must be considered. In contrast to cases of otherwise healthy women with menorrhagia, this is problematic in transplant patients, a group of women who are often poor surgical candidates as a result of overall morbidity or anticipated prolonged leukopenia and pancytopenia. Potential options that were discussed in this case included hysterectomy, hysteroscopic resection of the submucosal fibroid, uterine artery embolization, and endometrial ablation. The immediacy of transplant precluded hysterectomy or hysteroscopic surgery because of a concern that a protracted recovery might delay timely HSC transplant. Additionally, the patient's severe thrombocytopenia would have placed her at high risk for surgical and postoperative blood loss. Uterine artery embolization was not pursued because it is not an appropriate treatment for acute bleeding nor for a submucosal leiomyoma. Endometrial ablation was felt to be the least invasive and safest option if nonsurgical interventions continued to fail, but fortunately that was not the case.

We found that balloon tamponade was an effective alternative to surgery for the control of uterine hemorrhage requiring repeated transfusions. Balloon tamponade is a commonly used technique in managing postpartum hemorrhage and, compared with the surgical

interventions mentioned, carries less risk of morbidity and preserves the potential for childbearing for transplant patients.

The ultimate goal is to safely manage these patients through HSC transplant. Gynecologists consulted for menses suppression should be aware of the complexities and options for management in the peritransplant period. Additionally, health care practitioners should appreciate the importance, and difficulty, of quantifying bleeding in these patients who have such limited reserve. Because the primary management is often by a health care provider other than the gynecologist, it is important to consider transfusion requirements as a measure of success of medical therapy. This case illustrates that when medical therapy fails and surgery is contraindicated, balloon tamponade may be an additional, and potentially life-saving, strategy for control of uterine hemorrhage before HSC transplant.

Acknowledgments

Funded, in part, by the Intramural Program of the National Institutes of Health, National Institute of Allergy and Infectious Diseases, National Cancer Institute, Clinical Center, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Institutes of Health Intramural Office of Rare Diseases, the National Human Genome Research Institute, and clinical trials NCT00018044 and NCT00923364.

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