

Hormonal Therapy After Stem Cell Transplantation and the Risk of Venous-occlusive Disease

To the Editor:

The elegant report from Hagglund et al¹ recently published in *Blood* raises a very important ethical issue in clinical hematology practice: *primum non nocere*. The authors describe the impact of norethisterone treatment, routinely used in the prevention of menstrual bleeding in women submitted to allogeneic bone marrow transplantation, on veno-occlusive disease, which is one of most dreadful complications of an otherwise successful stem cell transplantation (SCT). This is an example of how we can interfere dramatically on the outcome of transplantation by simply adding an unsafe drug to the corollary of what we call "supportive treatment." Nevertheless, the management of menstrual bleeding during the phase of thrombocytopenia in premenopausal women may still be troublesome and requires specific treatment, particularly when concomitant gynecological disorders are present (ie, uterine fibromyomata or dysfunctional bleeding), and the use of estrogen-progestinics should be clearly avoided. Estrogen-progestinics may induce liver toxicity, primarily intrahepatic cholestasis and transaminitis,² and they also interfere with hemostasis through a reduction in the natural anticoagulant protein S and an increase in factor II levels inducing a thrombophilic state, which may be further amplified by genetically determined prothrombotic defects that occur fairly commonly in the general population. These defects include activated protein C resistance related to factor V Leiden, factor II G20210 A mutation, or antithrombin III deficiency.³⁻⁵

Therefore, in 1993 we started using a luteinizing hormone-releasing hormone analogue (LHRH) in a pilot study for the prevention of uterine bleeding in premenopausal women undergoing SCT.⁶ LHRH analogues induce a profound amenorrhea through the suppression of the pituitary-gonadal axis, do not interfere with the hemostatic balance,⁷ and do not cause liver toxicity. With leuprorelin acetate we have currently treated 47 consecutive premenopausal women submitted to SCT with no episodes of amenorrhea lasting more than 6 months and sexual hormone levels in the nonmenopausal range. Informed consent was obtained from all patients or guardians after discussion with the consultant gynecologist. The median age was 33 (range, 17 to 52) years. Diagnoses were acute myeloid leukemia (15), acute lymphoblastic leukemia Ph⁺ (3), non-Hodgkin's lymphoma (11), Hodgkin's disease (11), multiple myeloma (2), chronic myeloid leukemia (4), and RAEB-T (1). Thirty-one patients were submitted to allogeneic SCT from HLA-identical donors while the remaining 16 patients were submitted to autologous SCT. Conditioning regimen consisted of busulfan 4 mg/kg on 4 consecutive days and cyclophosphamide 60 mg/kg for 2 days in 33 patients, busulfan 4 mg/kg on 4 consecutive days and melphalan 90 mg/kg for 1 day in 5 patients, and BEAM in 9 patients. Graft-versus-host disease prophylaxis in the allogeneic SCT group was cyclosporine A and methotrexate. Leuprorelin depot was administered at the dose of 3.75 mg as a subcutaneous injection at least 30 days before the conditioning regimen, and a second injection was administered 28 days after the first dose. Venous-occlusive disease was not observed in these patients despite the fact that busulfan-containing conditioning

regimen was predominantly used. Only 2 of 47 patients (4.2%) developed mild uterine bleeding during thrombocytopenia. Thus, a profound amenorrhea was obtained in the majority of patients without additional toxicity. Therefore, we strongly agree with the recommendations of Hagglund et al for concern in the use of norethisterone or analogues in women undergoing SCT, but we do recommend the use of LHRH analogues for the management and prophylaxis of uterine bleeding, which should not be ignored after SCT.

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Is Complicated Celiac Disease or Refractory Sprue an Intestinal Intra-Epithelial Cryptic T-Cell Lymphoma?

To the Editor:

We have read with interest the report by Carbonnel et al¹ which suggests that complicated celiac disease (CD) is a form of cryptic T-cell lymphoma in four patients. We have recently published a similar study

of six patients with complicated CD, which we classified as refractory sprue,² in which we not only suggested a possible T-cell lymphomatous origin, but also showed that the clonal population was derived from intra-epithelial lymphocytes (IEL), based on the following observations: