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ORIGINAL ARTICLE

Ovarian recovery after stem cell transplantation

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Autologous or allogeneic SCT with conventional conditioning (chemotherapy with or without irradiation) has emerged as an effective and potentially curative therapy in patients with hematologic malignancies and in other selected solid tumors; however, several patients experience significant early and delayed side effects, including long-term endocrine imbalance and infertility. In spite of several reproductive recovery and pregnancy reports published in the oncology literature, review of medical literature reveals a paucity of comparable information in the SCT field. We report here four cases of ovarian recovery in patients who received hormonal replacement therapy after diagnosis of primary ovarian failure due to high-dose chemotherapy and SCT.

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Introduction

The use of SCT has become increasingly popular since the mid- to late 1980s for the treatment of leukemia and other malignant and nonmalignant disorders and has greatly enhanced patients' life expectancy. However, most pre-transplant conditioning protocols for SCT include alkylating agents, irradiation or both, causing premature ovarian failure due to the massive destruction of ova and ovarian follicular elements.[1,2] Thus, the issues of premature menopause, fertility and pregnancy become important components to be addressed in the management of these patients. Previously, spontaneous pregnancy after myeloablative conditioning for autologous or allogeneic SCT has been reported.[3,4] Here, we describe four patients achieving successful pregnancy following primary ovarian failure after SCT treated with hormonal replacement therapy (HRT). The cases reported here suggest the significance of HRT in alleviating post-menopausal symptoms, recovery of ovarian function and potentially restoration of fertility in young women receiving high-dose chemotherapy.

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Materials and methods

Patient 1
A 26-year-old woman was diagnosed with chronic myelogenous leukemia in chronic phase at the age of 15 years. She underwent allogeneic SCT from a matched sibling donor with BU and cyclophosphamide as the conditioning regimen. Subsequently, she developed grade II acute GVHD and was treated with cyclosporine and prednisone. At the age of 18, hematological relapse was diagnosed on day +1350 post-SCT and she received hydroxyurea (1.5 g/day), donor leukocyte infusion (DLI) and α-interferon. Following these treatments, she achieved hematological and molecular remission as demonstrated by a negative PCR for bcr/abl and remained in remission since then (8 years follow-up). Her post-DLI course was complicated by grade IV skin GVHD. Shortly after SCT, the patient developed amenorrhea, which continued post-DLI. She also noted symptoms of frequent hot flashes and musculoskeletal pain in her back and extremities as well as extreme fatigue. Laboratory tests demonstrated persistently high serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels, consistent with primary ovarian failure. A gynecological examination showed severe uterine, vaginal and breast atrophy. Following consultation with Reproductive Medicine specialists, she was started on HRT. She noted significant improvement in her symptoms within 2–3 weeks of starting the therapy and developed secondary sexual characteristics, such as breast tissue and pubic hair. Her menses resumed 32 months after initiation of HRT and at age 23, she gave birth to a healthy child.

Patient 2
A 26-year-old woman was diagnosed with Hodgkin's disease, nodular sclerosis type; stage IV-B at the age of 19 years. She received eight cycles of ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) and radiotherapy in involved areas. She did not achieve CR and therefore

received two additional cycles of DHAP (dexamethasone, cisplatin and cytarabine) followed by autologous SCT conditioned with BEAM (carmustine, etoposide, cytarabine and melphalan). Before SCT, patient received a standard dose of 3.75 mg depot leuprolide acetate (LH–RH agonist), subcutaneously. Shortly after receiving SCT she developed amenorrhea and was diagnosed with primary ovarian failure (FSH 65.8 mIU/ml). The patient was started on HRT with conjugated estrogens and medroxyprogesterone post-SCT and continued for 4 months, recovering spontaneous menstrual cycles 3 months after the initiation of HRT. At the age of 24 years, 30 months after HRT, she became pregnant and gave birth to a healthy child. As per now her disease is in remission and she continues to use oral contraceptives.

Patient 3

A 36-year-old woman was diagnosed with Hodgkin's disease nodular sclerosis type, stage III-A at the age of 28 years. She received six cycles of ABVD and two cycles of DHAP followed by autologous SCT conditioned with BEAM. Within a year of autologous SCT she had progression of disease and received radiation to mediastinum. Three years after diagnosis she became pregnant and delivered a healthy child following normal pregnancy. Two years after giving birth, she relapsed and was treated with two cycles of MIFAP (mitoxantrone, fludarabine, cytarabine and cisplatin). She received leuprolide acetate followed by continuous desogestrel and subsequently resumed normal menstrual periods. The patient continues to use oral contraceptives and does not experience postmenopausal symptoms.

Patient 4

A 26-year-old woman was diagnosed with diffuse Hodgkin's disease with bone involvement (stage IV) at the age of 19 years. She was treated with 10 weeks of VACOP-B protocol (etoposide, doxorubicin, CY, VCR, prednisone and bleomycin) without significant response. Therefore, she received CY for stem cell mobilization, followed by etoposide and received autologous SCT with BEAM conditioning (carmustine, etoposide, cytarabine and melphalan). The leuprolide acetate was initiated before the first chemotherapy and was used for 8 months until the SCT. Ten months following SCT, patient's amenorrhea persisted and she was diagnosed with primary ovarian failure. Since the patient presented with pulmonary thromboembolism 1 month after the SCT, HRT was not initiated at that time. One year post-SCT she continued to have postmenopausal symptoms, and HRT with estradiol plus noretisterone acetate was initiated and used for a total of 30 months. The patient became pregnant eight months following HRT and gave birth to a healthy child.

Patient no. 1 was treated in the Blood and Marrow Transplant Program at University of California San Diego (UCSD). Patient no. 2, 3 and 4 were treated at the Bone Marrow Transplantation Unit of the Ribeirao Preto Medical School, University of Sao Paulo, Brazil.

Discussion

Ovarian failure is a common complication following ablative chemotherapy/radiation for SCT, affecting over 90% of women. [1,2] In addition to the direct toxicity to the ovary by the cytotoxic agents and radiation, complications of SCT, including imbalance of the hypothalamic–pituitary–gonadal axis, may also affect ovarian function.[5,6] Among the different conditioning regimens for allogeneic SCT, TBI is the greatest risk factor of ovarian failure. Virtually 100% of the women of child-bearing age who undergo SCT with TBI will develop an ovarian failure.[7] Factors indicated in the development of ovarian failure are: (i) initial dose of chemotherapeutic agents, (ii) duration of administration and (iii) the total dosages received. The source of stem cells does not seem to play a role. High-dose myeloablative therapy with alkylating agents in the context of SCT is a poor risk factor for developing ovarian failure. The combination of high-dose BU and CY is one of the most potent conditioning regimens to induce an ovarian failure.[8] For patients who receive the same conditioning regimen age is the most significant factor in the development of ovarian failure.[9]

Women affected by primary ovarian failure typically present with amenorrhea, elevated gonadotropins and reduced estradiol levels. In addition, most affected women notice distressing menopausal symptoms, which are frequently reported as hot flashes, sleep/mood disturbances, dyspareunia and musculoskeletal pain.[10] Ovarian failure is associated with an increased risk of osteoporosis, cardiovascular disease and dementia.[10] Once menopausal symptoms start or gonadotropin levels suggest ovarian failure, treatment with HRT should begin promptly to prevent the early and late unwanted effects related to estrogen deficiency.[11] Because of the potential risks associated with HRT like breast cancer, stroke and venous thromboembolism, it is recommended that all women taking HRT be evaluated on an annual basis.[12,13] HRT can be administered in a variety of ways, including tablets, patches, implants, vaginal pessaries, gels and creams. The usual method of administering HRT is to start with lowest dose and gradually increase it until the menopausal symptoms are relieved. Recently, Leuprolide acetate, a gonadotrophin-release hormonal agonist (GnRHa) has been employed to protect ovarian function of women submitted to high-dose chemo- or radiation therapy.[14] Leuprolide acetate may induce ovarian protection as a result of ovarian suppression, by creating decreased ovarian perfusion, resulting in the diminished exposure of the ovaries to chemotherapeutic agents.[15] It is also possible that GnRH analogs may exert direct protective effect on the ovary via peripheral GnRH receptors, which have been documented on human granulosa cells found in the developing and mature follicles.[16] However, there is lack of consistent reports from pilot human clinical studies and the benefit of ovarian protection by GnRHa is still unproven. There are limited prospective data and randomized controlled studies in humans, which are flawed by short-term follow-up and lack of controls. Further trials are needed to validate clinical potential of GnRH in the preservation of fertility.[17–20]

In spite of the fact that almost all women who undergo BMT have developed an ovarian failure, recovery is possible. A large retrospective survey of fertility after SCT involving 37 362 patients revealed that only 0.6% of patients conceived after one autologous or allogeneic SCT.[21] Several studies have demonstrated that younger age (<25 years) at SCT is an important predictor of ovarian function recovery.[4,6] A single transplant procedure is associated with a higher fertility potential than a double transplant.[22] Specifically, certain chemotherapeutic regimens, which are possibly less gonadotoxic, may be more conducive to reproductive rescue.[22] TBI has also been shown to be associated with a 2- to 3-fold lower probability of regaining normal ovarian function.[9] Additionally, allogeneic SCT was considered a negative predictor of ovarian function recovery. However, recent study comparing ovarian function in patients treated with the same conditioning regimen for both autologous and allogeneic SCT without TBI did not show a statistically different outcome with allogeneic SCT in respect to the recovery of ovarian function.[6] Successful pregnancies in women after SCT are well documented.[3,23,24] Similarly, a recent study showed that 85% of pregnancies after SCT resulted in live births.[21] A large cohort study by Sanders *et al*.[4] showed that out of 708 post-pubertal women, 110 resumed normal ovarian function, of which only 32 subsequently became pregnant. Thus, the question remains, whether the use of HRT after high-dose chemotherapy may increase childbearing potential of these women. Only 0.82% of the offspring of SCT patients had severe congenital anomalies, developmental delay and malignant disease, a rate not higher than that reported in the general population. Allograft recipients are at higher risk of preterm deliveries, low birth weight infants and cesarean sections. Other investigators reported an increased risk of spontaneous abortion in women treated with SCT and TBI.[4]

Recovery of normal ovarian function with its associated ovulation, and even a viable pregnancy, is a realistic possibility in patients placed on HRT following premature ovarian failure induced by high-dose chemotherapy/radiation used to condition for an autologous or allogeneic SCT. The potential therapeutic interventions currently utilized for protecting and restoring infertility include: GnRHa, *in vitro* fertilization (IVF) using superovulation and embryo cryopreservation (the most commonly used method), ovarian tissue cryopreservation, or oocyte freezing.[25] Therefore, all sexually active recipients of SCT should receive counseling regarding pregnancy prior to the initiation of high-dose chemotherapy. Likewise, patients must be counseled on the use of effective birth control measures to prevent unwanted pregnancies, especially when subsequent treatment involves possibly teratogenic drugs.

References

1 Appelbaum FR, Herzig GP, Ziegler JL, Graw RG, Levine AS, Deisseroth AB. Successful engraftment of cryopreserved autologous bone marrow in patients with malignant lymphoma. *Blood* 1978; **52**: 85–95.
2 Schimmer AD, Quatermain M, Imrie K, Ali V, McCrae J, Stewart K *et al*. Ovarian function after autologous bone marrow transplantation. *J Clin Oncol* 1998; **16**: 2359–2363.
3 Gulati SC, Poznak CV. Pregnancy after bone marrow transplantation. *J Clin Oncol* 1998; **16**: 1978–1985.
4 Sanders JE, Hawley J, Levy W, Gooley T, Buckner CD, Deeg HJ *et al*. Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. *Blood* 1996; **87**: 3045–3052.
5 Tauchmanova L, Selleri C, Rosa GD, Pagano L, Orio F, Lombardi G *et al*. High prevalence of endocrine dysfunction in long-term survivors after allogeneic bone marrow transplantation for hematologic diseases. *Cancer* 2002; **95**: 1076–1084.
6 Tauchmanova L, Selleri C, Rosa GD, Esposito M, Palomba S, Bifulco G *et al*. Gonadal status in reproductive age women after hematopoietic stem cell transplantation for hematological malignancies. *Hum Reprod* 2003; **18**: 1410–1416.
7 Sklar C. Growth and endocrine disturbances after bone marrow transplantation in childhood. *Acta Paediatr* 1995; **411** (Suppl): 57–61.
8 Brennan BMD, Shalet SM. Endocrine late effects after bone marrow transplant. *Br J Haematol* 2002; **118**: 58–66.
9 Sanders JE, Buckner CD, Amos D, Levy W, Appelbaum FR, Doney K *et al*. Ovarian function following marrow transplantation for aplastic anemia or leukemia. *J Clin Oncol* 1988; **6**: 813–818.
10 Piccioni P, Scirpa P, D'Emilio I, Sora F, Scarciglia M, Laurenti L *et al*. Hormonal replacement therapy after stem cell transplantation. *Maturitas* 2004; **49**: 327–333.
11 Apperley JF, Reddy N. Mechanism and management of treatment-related gonadal failure in recipients of high dose chemo radiotherapy. *Blood Rev* 1995; **9**: 93–116.
12 Beral V, Banks E, Reeves G. Evidence from randomised trials on the long-term effects of hormone replacement therapy. *Lancet* 2002; **360**: 942.
13 Miller J, Chan BK, Nelson HD. Postmenopausal estrogen replacement and risk for venous thromboembolism: a systematic review and meta-analysis for the US Preventive Services Task Force. *Ann Intern Med* 2002; **136**: 680–690.
14 Somers EC, Marder W, Christman GM, Ognevovski V, McCune WJ. Use of gonadotrophin-releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. *Arthritis Rheum* 2005; **52**: 2761–2767.
15 Blumenfeld Z. Gynaecologic concerns for young women exposed to gonadotoxic chemotherapy. *Curr Opin Obstet Gynecol* 2003; **15**: 359–370.
16 Peng C, Fan NC, Ligier M, Vaananen J, Leung PC. Expression and regulation of gonadotropin-releasing hormone (GnRH) and GnRH receptor messenger ribonucleic acids in human granulose luteal cells. *Endocrinology* 1994; **135**: 1740–1746.
17 Blumenfeld Z, Avivi I, Linn S, Epelbaum R, Shahar BM, Haim N. Prevention of irreversible chemotherapy-induced ovarian damage in young women with lymphoma by a gonadotrophin-releasing hormone agonist in parallel to chemotherapy. *Hum Reprod* 1996; **11**: 1620–1626.
18 Blumenfeld Z, Avivi I, Ritter M, Rowe MJ. Preservation of fertility and ovarian function and minimizing chemotherapy-induced gonadotoxicity in young women. *J Soc Gynecol Investig* 1999; **6**: 229–239.
19 Recchia F, Sica G, De Filippis S, Saqqio G, Rosselli M, Rea S. Goserelin as ovarian protection in the adjuvant treatment of premenopausal breast cancer: a phase II pilot study. *Anticancer Drugs* 2002; **13**: 417–424.
20 Franke HR, Smit WM, Vermes I. Gonadal protection by a gonadotropin-releasing hormone agonist depot in young women with Hodgkin's disease undergoing chemotherapy. *Gynecol Endocrinol* 2005; **20**: 274–278.

21 Salooja N, Szydlo RM, Socie G, Rio B, Chatterjee R, Ljungman P *et al*. Pregnancy outcomes after peripheral blood or bone marrow transplantation: a retrospective survey. *Lancet* 2001; **358**: 271–277.
22 Salooja N, Chatterjee R, McMillan AK, Kelsey SM, Newland AC, Milligan DW *et al* Successful pregnancies in women following single auto transplant for acute myeloid leukemia with a chemotherapy ablation protocol. *Bone Marrow Transplant* 1994; **13**: 431–435.
23 Jackson GH, Wood A, Taylor PR, Lennard AL, Lucraft H, Heppleston A *et al*. Early high-dose chemotherapy intensification with autologous bone marrow transplantation in lymphoma associated with retention of fertility and normal pregnancies in females. Scotland and Newcastle lymphoma group, UK. *Leuk Lymphoma* 1997; **28**: 127–132.
24 Brice P, Haioun C, Andre M, Gisselbrecht C. Pregnancies after high-dose chemotherapy and autologous stem cell transplantation in aggressive lymphoma. *Blood* 2002; **100**: 736.
25 Chatterjee R, Kottaridis PD. Treatment of gonadal damage in recipients of allogeneic or autologous transplantation for hematological malignancies. *Bone Marrow Transplant* 2002; **30**: 629–635.