Original Study

Impact of Reduced-Intensity Conditioning Allogeneic Stem Cell Transplantation on Women's Fertility

Emmanuelle Assouline,[1] Roberto Crocchiolo,[2] Thomas Prebet,[2] Florence Broussais,[2] Diane Coso,[2] Marc Gamerre,[3] Norbert Vey,[2] Didier Blaise,[2] Blandine Courbiere[3,4]

Abstract

Allogeneic stem cell transplantation (Allo-SCT) after myeloablative conditioning causes premature ovarian failure (POF) in 95% to 100% of cases. We showed that despite the use of a reduced intensity conditioning (RIC) regimen, most patients (86.3%) had POF. Our data showed that after RIC Allo-SCT fertility seems to depend on previous cumulative doses of chemotherapeutic agents.

Introduction: Available data on women fertility for younger patients treated using RIC Allo-SCT are still limited. We evaluated ovarian function and fertility among female patients younger than 35 years who received RIC Allo-SCT for hematological malignancy or aplastic anemia (AA). **Patients and Methods:** Information on therapies before RIC Allo-SCT were collected. Data on ovarian function and fertility evaluation after RIC Allo-SCT included clinical and biological criteria. Twenty-two patients were evaluated. **Results:** After RIC Allo-SCT, amenorrhea affects 68.1% of patients. Ovarian function was impaired for 86.3% of cases. All 3 AA patients have regular cycles and became pregnant after RIC Allo-SCT. Only 6 (27.2%) patients declared to have been correctly informed before RIC Allo-SCT on potential deleterious effects on fertility of anticancer treatment and only 36.8% of patients with ovarian failure had a hormonal supplementation. **Conclusion:** Results showed a high rate of ovarian failure, evaluated by clinical and biological criteria. The difference between AA and malignant diseases might suggest that a potential deleterious role was played by previous anticancer treatments rather than by RIC Allo-SCT.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 13, No. 6, 704-10
Keywords: Allogeneic stem cell transplantation, Chemotherapy, Fertility preservation, Hormone replacement therapy Premature ovarian failure

Introduction

Allogeneic stem cell transplantation (Allo-SCT) is 1 of the potential curative options for several hematological diseases and might represent the only curative approach in some hematological malignancies. The number of Allo-SCTs has progressively increased worldwide[1] and the number of long-term survivors increased in parallel, raising the issue of long-term toxicities. For instance, intensive chemotherapy and/or radiotherapy used for conditioning regimens are associated with gonadic toxicity and might cause premature ovarian failure (POF) in younger patients.[2] POF is defined by a premature depletion of ovarian follicles before the age of 40 years and is characterized by secondary hypergonadotropic amenorrhea. After conventional allogeneic transplantation, rates of POF ranges from 95% to 100%,[3,4] and pregnancy rate is extremely low, ranging from 0.6% to 5.5% according to the studies.[5,6] Over the past 20 years, the use of reduced intensity conditioning (RIC) Allo-SCT has progressively increased. This approach is characterized by reduced doses of chemotherapy and/or radiotherapy, aiming at reducing short-term toxicities and allowing transplantation in patients for whom myeloablative conditioning is not feasible. This was mainly

[1]Department of Oncology, Institut Paoli-Calmettes, Marseille, France
[2]Department of Hematology, Institut Paoli-Calmettes, Marseille, France
[3]Department of Gynecology, Obstetrics, and Reproduction, AP-HM La Conception, Marseille, France
[4]Biogénotoxicologie, Santé Humaine & Environnement UMR 6116, IMBE, Aix-Marseille, Université, Aix-en-Provence, France

Submitted: Mar 3, 2013; Revised: May 13, 2013; Accepted: May 23, 2013; Epub: Sep 24, 2013

Address for correspondence: Emmanuelle Assouline, MD, Department of Oncology, Institut, Paoli-Calmettes, 232 bd Sainte Marguerite, 13273 Marseille Cedex 9, France Fax: 04-91-22-35-45; e-mail contact: assoulinee@ipc.unicancer.fr

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2013.05.014

developed for elderly patients but has also been used for younger patients. Interestingly, there are few data in the RIC Allo-SCT setting regarding gonadic toxicity in the youngest patients. Effects of chemotherapy and radiotherapy on ovarian function are dose-dependent[7] and the use of RIC Allo-SCT potentially reduces ovarian toxicity. The aim of this study was to evaluate ovarian function and fertility of patients undergoing RIC Allo-SCT, to better identify patients who are likely to develop POF, and to better counsel them. We also evaluated the information provided to patients about infertility risks and fertility preservation programs.

Patients and Methods

Patient Selection

Patients eligible for the analysis were female, aged 18-35 years, and treated between January 2000 and January 2010 for hematological disease at Institut Paoli-Calmettes (Marseille, France) with RIC or nonmyeloablative Allo-SCT[8] and alive at the last follow-up in August 2011. All patients gave their written informed consent for participation in the study, which was approved by the local Ethical Committee. Patients and transplant data were collected using electronic clinical records: disease, therapy lines before and after transplantation, conditioning regimen, and relapse after transplant if applicable. Cumulative doses of cyclophosphamide, melphalan, busulfan, and radiation were calculated. RIC and nonmyeloablative conditioning as elsewhere defined[8] are referred to as RIC herein. Transplants were performed using bone marrow, peripheral blood stem cells, or cord blood as stem cell sources. Donors were related (human leukocyte antigen-identical sibling) or 10/10-matched unrelated. Prophylaxis against pneumocystis jirovecii and toxoplasmosis consisted of trimethoprim-sulfamethoxazol. Amoxicillin, valacyclovir, and fluconazole were administered as prophylaxis against encapsulated bacteria, herpes simplex virus, and candida. Patients were monitored for cytomegalovirus (CMV) reactivation during the first 6 months after transplant, and preemptive antiviral therapy was given if CMV reactivation occurred.

Ovarian Reserve Assessment After RIC Allo-SCT and Fertility Outcome

Data on ovarian function and fertility after RIC Allo-SCT were collected during gynecological consultation proposed systematically after the end of cancer treatments: menstrual cycles, and menopausal symptoms. Serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and anti-Müllerian hormone (AMH) were measured at day 2 or 3 of the cycle in patients with spontaneous menses or during amenorrhea in others. AMH was evaluated to best reflect quantitative ovarian reserve, because it has been shown that it is more sensitive than LH, FSH, or estradiol,[9] and not affected by menstrual cycle or oral contraception.[10] Biological assessment of ovarian reserve was not performed in pregnant patients after RIC Allo-SCT. Results are presented as median with ranges. We evaluated pregnancy rate, term delivery, mode of delivery, and the health of the child after RIC Allo-SCT. We also evaluated the prescription of hormone replacement therapy (HRT) or hormonal contraception (HC). Patients were also asked about impairment of ovarian function information and fertility preservation techniques received before RIC Allo-SCT.

Results

Patient Characteristics

A total of 96 patients aged 18 to 35 years underwent RIC Allo-SCT between January 2000 and January 2010. Fifty patients were alive when the study started, and 23 were female patients selected for the analysis. One patient was lost to follow-up. Therefore, a total of 22 patients were included in our study. One patient died after inclusion because of chronic graft vs. host disease (GvHD). Median follow-up from RIC Allo-SCT was 50 months (range, 5-93 months). Median age at last follow-up was 32.5 years (range, 22-46 months); median age at transplantation was 27 years (range, 18-35 years). Main patient and transplant characteristics are detailed in Tables 1 and 2.

In 23 patients, 8 patients (36%) were treated for Hodgkin lymphoma, 5 patients (23%) for acute myeloid leukemia, 3 patients (14%) for aplastic anemia (AA), 2 patients (9%) for acute lymphoid leukemia, 2 patients (9%) for multiple myeloma, 1 patient (4.5%) for non-Hodgkin lymphoma, and 1 patient (4.5%) for chronic lymphoid leukemia. Except the 3 cases of AA, all patients received chemotherapy before RIC Allo-SCT: 27% of patients had received 1 previous line of chemotherapy, 32% had received 2 lines, and 27% had received 3 lines or more (Table 1). One had received subdiaphragmatic radiotherapy. Autologous transplant with BEAM (carmustine, etoposide, aracytine, and melphalan) conditioning or high-dose melphalan (140 or 200 mg/m^2) was performed in 45.4% of the patients. A combination of fludarabine 150 to 180 mg/m^2 total dose, either oral busulfan 8 mg/kg or intravenous formulation 6.4 mg/kg, and antithymocyte globulin (ATG) 2.5 to 7.5 mg/kg was administered to 10 patients and fludarabine 200 mg/m^2, cyclophosphamide 50 mg/kg, and total body irradiation (TBI) 2 Gy to 4 patients. Other conditioning regimens were: cyclophosphamide 200 mg/kg and ATG 12.5 mg/kg (n = 3), TBI 2 Gy either alone (n = 1) or in combination with fludarabine 90 mg/m^2 (n = 3), or fludarabine and rituximab (n = 1) (Table 1). Cyclosporine alone or in combination with mycophenolate mofetil was used as GvHD prophylaxis according to local guidelines or protocols.[11] At the time of the study, 77.3% of patients were in persisting remission and 22.7% relapsed with 2 patients treated with chemotherapy and 2 with immunotherapy. Regarding the gynecologic characteristics of the population, median age of first menstruation was 13 years. Before any oncological treatment, 86.3% of the patients presented with regular menstrual cycles, and 59% had already been pregnant (Table 2).

Ovarian Reserve Assessment After RIC Allo-SCT and Fertility Outcome

Fifteen patients (68.1%) were in amenorrhea at last contact. Eight out of these (53%) were already in amenorrhea because of POF before RIC Allo-SCT. Seven patients presented spontaneous menses. Three patients diagnosed with AA continued to have regular menstrual cycles. Three patients, diagnosed with hematological malignancy, had irregular menses, reappearing 6 months, 1 year, and 6 years after Allo-SCT. In 1 patient, menstrual bleedings were attributed to hematocolpos because of vaginal chronic GvHD. Among the 15 patients with amenorrhea, 13 presented vasomotor symptoms with hot flashes. Serum hormonal levels were measured in 14 out of 19 patients with hematological malignancy. Despite the presence of spontaneous menstrual cycles in 3 patients, a