The Oncologist®

The Community Oncologist: Case Report

Repeated Spontaneous Pregnancies and Successful Deliveries After Repeated Autologous Stem Cell Transplantation and GnRH-Agonist Treatment

ZEEV BLUMENFELD, TSILA ZUCKERMAN

Rambam Health Care Campus and Technion, Faculty of Medicine, Haifa, Israel

Disclosures: Zeev Blumenfeld: None; **Tsila Zuckerman:** None.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the authors or independent peer reviewers.

Two years ago we published an exceptional case [1] of a young patient who successfully delivered a healthy neonate after spontaneous conception despite two (repeated) stem cell transplantations and aggressive conditioning chemotherapy in parallel with monthly gonadotropin-releasing hormone agonist (GnRH-a) cotreatment (Decapeptyl CR, 3.75 mg; Ferring, Saint-Prex, Switzerland) and irradiation for lymphoma [1]. Against all the odds, this patient conceived again and again delivered a second normal neonate, most probably attributable to the GnRH-a cotreatment during chemotherapy.

In brief, this young woman received chemotherapy and, in parallel, monthly depot GnRH-a injections in 1995 when she was 15 years old for stage IV anaplastic lymphoma [1]. Less than 1 year afterward she underwent autologous stem cell transplantation (SCT) with carmustine, etoposide, cytarabine, and cyclophosphamide (the BEAC protocol) for persistent disease [1], again with GnRH-a pre- and cotreatment during chemotherapy [1–3]. Her first spontaneous pregnancy occurred at the age of 24 years, but that pregnancy ended in miscarriage. One month later, she conceived again, and that pregnancy developed normally until 25 weeks of gestation, when recurrence of the lymphoma was diagnosed with subsequent intrauterine growth retardation and demise, after dexamethasone, etoposide, ifosfamide, and cisplatin (DVIP) chemotherapy during pregnancy [1]. After pregnancy termination, she again received a GnRH-a in parallel with DVIP and BEAC conditioning, followed by a second autologous SCT. An attempt at in vitro fertilization was discontinued because of a poor response, but 3 months later she spontaneously conceived, and after a normal gestation she delivered, in August 2006, a normal, term, 3,450 gram, female neonate [1]. About 1 year later she spontaneously conceived, for the fourth time, and on August 9, 2008 she again successfully delivered a normal, 3,450 gram, female neonate, with an Apgar score of 10 at 5 minutes.

SCT almost invariably induces ovarian failure, irrespective of patient age or treatment protocol [1, 4–6]. Only 0.6% of patients conceive after one autologous or allogeneic SCT, according to a large survey on fertility after SCT, involving 37,362 women [5]. The estimated odds for spontaneous conception after two SCTs are negligible ($0.006 \times 0.006 = 0.000036$) [1, 3–5]. Carter et al. [6] conducted a retrospective study on reproductive function and pregnancy outcomes in 619 women and partners of men treated with

Correspondence: Zeev Blumenfeld, M.D., Department of Obstetrics and Gynecology, Rambam Medical Center, Technion-Faculty of Medicine, Haifa 31096, Israel. Telephone: 972-4-8542577; Fax: 972-4-8543746; e-mail: bzeev@techunix.technion.ac.il, z_blumenfeld@rambam.health.gov.il Received November 1, 2009; accepted for publication December 9, 2009; first published online in *The Oncologist Express* on January 12, 2010. 1083-7159/2010/$30.00/0 doi: 10.1634/theoncologist.2009-0269

autologous or allogeneic hematopoietic SCT. They found that only 3% of their female survivors succeeded in conceiving after one SCT [6]. Thus, theoretically, according to their findings, the estimated odds for spontaneous conception after two SCTs are $0.03 \times 0.03 = 0.0009$, which is <1: 1,000. Although several reports on spontaneous conceptions and deliveries after SCT have been published [7], we are not aware of any publication of repeated successful deliveries after repeated SCT in the same patient. To the best of our knowledge, this is the first case.

The administration of a GnRH-a before and in parallel with chemotherapy simulates a prepubertal hormonal milieu, and through this mechanism, and/or possibly others [1–3], might have minimized the gonadotoxic effect of chemotherapy and increased the chance of spontaneous ovulations and successful conceptions and deliveries [1–3]. Indeed, similarly, Remérand et al. [8] recently reported on four successful pregnancies in a patient who had been treated with allogeneic bone marrow transplantation when she was 4 years old. GnRH-a treatment simulates the prepubertal hormonal milieu, in keeping with our patient's recent repeated spontaneous gestation, despite SCT [8]. Because most of the methods involving ovarian or egg cryopreservation are not yet clinically established and unequivocally successful, physicians should inform these young women of the possible beneficial effect of a GnRH-a in minimizing gonadal damage and preservation of ovarian function and fertility, in addition to the options of cryopreservation of embryos and ova [1–3].

Author Contributions

Conception/Design: Zeev Blumenfeld, Tsila Zuckerman
Administrative support: Zeev Blumenfeld, Tsila Zuckerman
Provision of study material or patients: Zeev Blumenfeld, Tsila Zuckerman
Collection and/or assembly of data: Zeev Blumenfeld, Tsila Zuckerman
Data analysis and interpretation: Zeev Blumenfeld, Tsila Zuckerman
Manuscript writing: Zeev Blumenfeld, Tsila Zuckerman
Final approval of manuscript: Zeev Blumenfeld, Tsila Zuckerman

References

1 Blumenfeld Z, Benaroush M, Zuckerman T. Spontaneous pregnancy and normal delivery after repeated autologous bone marrow transplantation and GnRH agonist treatment. Hum Reprod 2007;22:2346.

2 Blumenfeld Z, Avivi I, Eckman A et al. Gonadotropin-releasing hormone agonist decreases chemotherapy-induced gonadotoxicity and premature ovarian failure in young female patients with Hodgkin lymphoma. Fertil Steril 2008;89:166–173.

3 Blumenfeld Z. How to preserve fertility in young women exposed to chemotherapy? The role of GnRH agonist cotreatment in addition to cryopreservation of embrya, oocytes, or ovaries. ***The Oncologist*** 2007;12: 1044–1054.

4 Lobo RA. Potential options for preservation of fertility in women. N Engl J Med 2005;353:64–73.

5 Salooja N, Szydlo RM, Socie G et al. Pregnancy outcomes after peripheral blood or bone marrow transplantation: A retrospective survey. The Lancet 2001;358:271–276.

6 Carter A, Robison LL, Francisco L et al. Prevalence of conception and pregnancy outcomes after hematopoietic cell transplantation: Report from the Bone Marrow Transplant Survivor Study. Bone Marrow Transplant 2006;37:1023–1029.

7 Matias K, Matias C, Teixeira H et al. Successful pregnancy following busulfan and cyclophosphamide conditioning and allogeneic bone marrow transplantation for chronic myeloid leukemia. Biol Blood Marrow Transplant 2008;14:944–945.

8 Remérand G, Merlin E, Froissart R et al. Four successful pregnancies in a patient with mucopolysaccharidosis type I treated by allogeneic bone marrow transplantation. J Inherit Metab Dis 2009 Mar 13 [Epub ahead of print].