SYMPOSIUM

Impact on Fertility in Patients with Hematological Malignancies and Bone Marrow Transplant

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Abstract

With the rapidly improving outcome of patients suffering from hematologic disorders and cancers, there exists a rapidly widening gap of unmet need regarding fertility preservation in this group. Hematologic cancers make for a large proportion of all cancers in young patients and there are issues peculiar to hematologic neoplasms which are not observed by the patients suffering from solid tumors. The biggest challenge is seen with the patients undergoing hematologic stem cell transplants because it involves use of high doses of cytotoxic chemotherapy with or without radiation. In majority of these cases, the damage to gonadal function is irreversible. Each hematologic disorder in young patients poses a unique challenge regarding fertility preservation. In this review, we address some important aspects related to fertility in patients suffering from a few selected hematologic disorders.

Keywords: Bone marrow transplant, Cancer, Chemotherapy, Fertility, Hematology, Preservation.

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Introduction

In the last few decades, the field of hematology–oncology and bone marrow transplant (BMT) has seen tremendous growth. From the era of few chemotherapeutic agents, now we live in an era of multi-targeted therapies, immunologic therapies, and complex types of stem cell transplants.

These advances have led to increase in number of cancer patients who survive their primary illness and live a long post treatment life.[1] However, the same has also resulted in rising number of survivors who are leading an otherwise normal life but facing difficulty in conception and pregnancy. Fertility-related difficulties faced by cancer survivors can be a reason of significant stress and anxiety which may further compromise their quality of life.

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Impact of Treatment Used in Hemato-oncology and BMT on Fertility

The main group of treatment used in hematology and BMT which affect fertility are alkylating agents and radiation. The alkylating agents like cyclophosphamide, dacarbazine, cisplatin, and ifosfamide, etc., are commonly used drugs in hematology. In the field of BMT, drugs like nitrosoureas, melphalan, and busulfan, etc., along with total body irradiation are commonly used and all of them are known to produce irreversible injury to gonads and gametogenesis.

In testes, the reproductive function depends on sertloli cells in nourishing and supporting role, leydig cells as a source of testosterone, and germ cells as a producer of spermatozoa. Out of these three types of cells, the germ cells are highly sensitive to chemotherapy while leydig cells are relatively resistant to the same.[2]

Unlike the testes, ovaries have a fixed number of primordial follicles which mature cyclically to produce an ovum. The cytotoxic chemotherapy drugs have impact on all of these follicles and lead to depletion of immature oocytes as well as hormone producing cells.

The most common cancers in pediatric, adolescent, and young adult age group are hematologic cancers. Majority of these patients are either in their reproductive years or about to enter in the same. The survivors of these hematologic cancers in this age group would expect to get married and have children as a part of living a normal life.

Another issue related to fertility preservation in patients with hematologic cancers which make them different from other solid tumors is the very acute and sick state of patients at the time of diagnosis. Majority of the cases of leukemia and aggressive lymphoma need chemotherapy within a few days of diagnosis, and in most of the cases, it would not allow sufficient time for fertility preservation or gametocyte preservation procedures.

There are more than 1 million post chemotherapy survivors of various leukemia and lymphoma in the United States.[3] At present we do not have similar national data in India; however, going by the population statistics, it can be estimated that around 3 million hematologic cancer survivors are currently living in India and a significant proportion of them face fertility-related issues. There will be approximately 242,000 survivors of hematopoietic cell transplant (HCT) by 2020, which accounts for roughly 1% of all survivors.[4] In the BMT survivor study, transplant recipients were 36 times more likely than siblings to report no conception.[5]

In the following sections, we discuss some issues specific to a few specific hematological conditions.

Acute Leukemia

Majority of acute myeloid leukemia (AML) patients are older and they are likely to have completed their family by the time of developing AML. Hence, issues related to fertility preservation are a lesser concern in AML patients than in acute lymphoblastic leukemia (ALL) patients.

ALL is the most common malignancy in prepubertal age group. More than half of all cases of ALL (56%) occur among people aged less than 20 years. The remission rate of ALL has been reported to be 95% among teenagers and 78–92% among adults in western population.[6]

The treatment of ALL includes combination of anticancer chemotherapy from various groups of anticancer drugs given over a period of 2–3 years. As majority of ALL patients are prepubertal, gametocytes cannot be stored due to their immature gonadal status. Likewise, gonadal tissue preservation remains experimental in this age group.[7]

Another notable aspect in leukemia patients is gonadotropism of malignant lymphoblasts. The testes and ovaries are sanctuary sites where malignant blasts may remain embedded at the time of gonadal tissue harvesting before starting chemotherapy. Therefore, a possible malignant cell contamination may pose a theoretical risk of relapse following use of this gonadal tissue in future.

Chronic Myeloid Leukemia

Majority of the patients of chronic myeloid leukemia (CML) present in chronic phase and they would need lifelong tyrosine kinase inhibitor (TKI) therapy like imatinib. These TKIs are FDA pregnancy category D drugs which means that there is evidence of fetal risk. Therefore, it is advisable to discuss this issue in reproductive age female CML patients at the time of starting first line TKI therapy.[8]

In 2019, we have evidence for successful discontinuation of TKI in patients of CML who have attained deep molecular response.[9] However, we would caution against stopping TKI only for the purpose of conceiving. The discontinuation of TKI needs to be practiced under supervision of a hemato-oncologist and it would need monthly monitoring of BCR-ABL transcript by reverse transcriptase-polymerase chain reaction (RQ-PCR). This treatment-free remission state can provide a clear window where a couple can plan to conceive without risk of TKI-related teratogenicity. The second option for these patients is use of IFN alpha instead of TKI during the phase of conception and first trimester of pregnancy.[10]

Lymphoma

Both Hodgkin's and non-Hodgkin's lymphoma have high cure rates with multiagent chemotherapy. The age of peak incidence of Hodgkin's lymphoma is in the second decade of life and around 80% of these patients will be cured with multiagent combination of chemotherapy.

This is a sizeable population in the field of hematology where fertility preservation remains an unmet need. Therapies containing alkylating agents like cyclophosphamide or procarbazine cause oligo/azoospermia in 90–100% of men under the age of 30 years. In women from similar cohort, the incidence of ovarian failure was found to be 5–25%.[11]

In the post-pubertal patients of Hodgkin's lymphoma, there is a small window for preservation of sperm/oocytes, and in selected cases, it may be permissible to adjust chemotherapy dates as per the need of fertility preservation procedure. However, the bigger challenge arises in patients who present with advanced stages of lymphoma or with more serious types of lymphoma demanding immediate treatment. Mostly, the practices used for preservation of fertility in patients with solid tumors may be applied in patients of lymphoma with some modification.

Hematopoietic Stem Cell Transplant

The treatment regimen used in stem cell transplant contains high doses of conventional chemotherapy as well as radiotherapy. Most of the patients who receive myeloablative conditioning regimen for transplant will experience infertility. As mentioned above, in a BMT survivor study, transplant recipients were 36 times more likely than siblings to report no conception.[5]

The probability of recovery of gonadal functions after these conditioning regimen is minimal. Therefore, all attempts should be made to preserve gametocyte/embryo before starting transplant procedure. This strategy can be highly successful for the patients undergoing stem cell transplant for benign diseases like aplastic anemia or immunodeficiency disorders. These patients are not exposed to chemotherapeutics drugs for their primary illness which enables collection of healthy gametocytes so that probability of successful fertilization remains high in future. The situation is much more complex in patients undergoing transplants for malignancies. Prior exposure to anticancer drugs leads to poorer quality of sperm/oocytes at the time of preservation before BMT. As a result, there may be difficulties with *in vitro* fertilization techniques in the future in these cancer patients.

The BMT is a curative treatment and the patients who survive initial transplant procedure are expected to live long life. Therefore, with increasing awareness among transplant physicians as well as with easy access to fertility preservation facilities, the transplant recipient subjects will be a sizeable population to serve for this unmet need.

Thalassemia

Recent advances in the field of iron chelation therapy and stem cell transplant have enabled a reasonable proportion of thalassemia major (TM) patients to enter reproductive age group. Spontaneous fertility is possible in only a minority of well chelated and transfused patients, while a majority of them would be infertile due to hypogonadotropic hypogonadism (HH).[12]

The major pathogenetic mechanisms for HH are related to pituitary hemosiderosis that impairs LH and FSH pulsatile secretion leading to low or absent stimulation of gonads, reducing the synthesis of sex hormones and the production of gametes. Moreover, the excess of free iron causes oxidative stress thereby impairing oocyte function.[13] Preservation of female fertility in patients with TM therefore requires appropriate chelation therapy from a young age with a view to maintain regular hormonal secretion and ovarian function. Clinical evaluation for infertile women with TM would involve documentation of anthropometric characteristics, evaluation of hemosiderosis-related cardiac and hepatic disease, and hematologic data of hemoglobin values and ferritin status. Besides a detailed gynecologic evaluation that includes menstrual history, hormonal profile for FSH, LH, estradiol, prolactin, anti-mullerian and thyroid hormones, and a pelvic ultrasound evaluating uterine size and antral follicle count is warranted. Treatment for amenorrhea and infertility due to HH includes hormone therapy with estrogen–progestin sequential treatment or oral contraceptives. Infertility therapies

are contraindicated in patients with significant cardiac iron overload (T2*MRI < 10 milliseconds) or hepatic iron overload (liver iron concentration >15 mg/g dry weight). In those women who are considered eligible for infertility therapy, first line therapy includes ovarian stimulation with gonadotropins with a pregnancy rates up to 70–72%. Up to 30% of TM women who fail ovarian stimulation may benefit from other advanced assisted reproduction techniques.[14]

Similar to women, prevention of male infertility therefore warrants maintenance of low iron levels from early childhood. In patients with established HH and oligozoospermia, testosterone production can be stimulated using human chorionic gonadotropin (hCG) or clomiphene up to 6 months prior to planning a child. Besides other assisted reproduction techniques include intracytoplasmic sperm injection (ICSI) or considering sperm cryopreservation at an early age.[15]

A unique aspect of thalassemia patient's fertility planning involves testing for thalassemia carrier state of the partner by Hb electrophoresis to minimize risk of having a child with thalassemia major. Ideally, it should be part of premarital testing and counselling. However, if in an already married couple if one partner has thalassemia major while the other partner is a thalassemia carrier then all attempts should be made for antenatal diagnosis of thalassemia major in the fetus.

Special Challenges in Fertility Preservation

- One lesser discussed aspect of fertility-related issues in cancer survivors is loss of libido. In a study from India, sexual dysfunction was observed in around 50% female cancer survivors.[16] In many cases, reduced libido results from body image issues and underlying affect disorders. However, in a significant number of cases, the loss of libido is due to endocrinologic reasons which results from reduced sex hormones in both males and females following chemotherapy. This specific aspect of infertility in cancer survivors needs a different approach than the conventional gamete preservation and *in vitro* fertilization techniques. We wish to sensitize the hematologist and oncologist about this aspect of cancer care because it is less likely to be reported by the patient.
- At present, majority of health insurance agencies do not cover the cost of fertility preservation procedures. It is imperative on the treating hematologists and oncologists to create awareness about the importance of this intervention as a part of whole cancer care. Such changes will need a large-scale patient advocacy, physicians support, and intervention from the government.

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