Fertility Management for the Hemato-Oncologist

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Abstract For cancer survivors, social parenthood buffers distress and improves quality of life. It is important that physicians dealing with treatment of malignancies are aware of this patient perspective. This review deals with risks of infertility with hematological malignancies and chemotherapy, modes of fertility preservation interventions, time and barriers to referral to specialists offering these interventions. This review aims to guide the hemato-oncologist to make an informed decision with the patient and the partner about fertility preservation at the right time.

Keywords Hematological malignancies · Infertility · Fertility preservation

Introduction

With the improvement in life expectancy following chemotherapy and stem cell transplantation, there is a better recognition of the problems associated with cancer survivors. Of these infertility occupies centre stage from the patient's perspective. Various quality of life surveys in cancer survivors have shown that ability to become a parent is associated with satisfactory quality of life (QOL). These surveys have also shown that reproductive concerns are associated with depression and distress [1]. The American Society of Clinical Oncology (ASCO) issued

guidelines in 2006 to the oncologists to refer all oncological patients for infertility management [2]. This guideline was updated in 2013 to include all health care providers [3]. National surveys of practice behaviours showed less than half of oncologists followed these guidelines [4]. Hematologists need to be aware of the fertility issues associated with chemotherapy and hematopoietic cell transplantation (HCT) and the ways to deal with them. The first part of this review aims to identify the target population at risk for infertility in haematological malignancies, the etio-pathogenesis of therapy induced gonadal failure. The second part of this review deals with the fertility preservation options, role of multidisciplinary team approach and reducing barriers in referral to fertility experts. The review concludes with a summary to enable the hemato-oncologist along with the patient and his/her partner make informed decisions about fertility preservation.

Target Population

The approximate percentage of patients with haematological malignancies who fall in the reproductive age group (Age < 50 years) is as summarized in Table 1. Of these patients a variable percentage of patients are cured of their disease. This will be the survivor population with the burden of infertility.

Therapy Induced Gonadal Failure (TIGF)

The risk of chemotherapy induced gonadal failure is not easy to define. The risk varies with time and severity from a transient gonadal insufficiency to premature gonadal

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Table 1 Target population for fertility preservation

Disease	Disease	Age < 50 years (%)	Cure rates (%)
Acute leukemia	Acute lymphoblastic leukemia (ALL)	75	40–90
	Acute myeloid leukemia (AML)	20	50–60
Lymphoma	Hodgkins lymphoma	64	80
	Non hodgkin lymphoma (NHL)	17	60
Chronic leukemia	Chronic myeloid leukemia (CML)	25	–
	Chronic lymphocytic leukemia (CLL)	Disease of elderly	–
Plasma cell dyscrasias	Multiple myeloma	Disease of elderly	–
Hematopoietic cell transplant (HCT)	Allogeneic	45	–
	Autologous	25	–

failure. There is a lack of a standard diagnostic criteria for gonadal failure and fertility recovery. Therefore, the exact incidence of gonadal failure is not known.

Pathogenesis of TIGF

The effect of therapy is different in each gender. Testicular function is dependent on the interaction between sertoli, leydig and germ cells. Cytotoxic therapy damages the rapidly dividing cells, leading to diminution of the germ cell pool, affecting spermatozoa production. Any therapy which leads total depletion of the spermatogonial stem cells will lead to permanent infertility. The leydig cells, which are responsible for testosterone production, are more resistant to chemotherapy [5].

Females are born with their full complement of oocyte which is gradually depleted. The therapy for cancer accelerates this process and leads to reduction in the fertile period and premature menopause. A study which followed women treated for cancer before the age of 20 years, found that 42% of the cases reached menopause by the age of 31 in comparison to 5% among the healthy controls [6].

Factors Affecting TIGF

The effect of therapy for cancer on the reproductive system is dependent on a number of factors.

1. *Host factors* Age is the most important host factory determining infertility. The risk of infertility is higher in the post pubertal period with some studies suggesting age of 30 as the cut-off for transplant patients [7]. But gonadotoxic therapy affects the fertility potential of children as well. The pre pubertal testis demonstrates significant activity, which is essential for normal adult testicular function [8]. Thus, children who receive cytotoxic therapy are also at risk of subsequent infertility. Both the timing in relation to puberty and nature of the gonadotoxic insult will influence the infertility rates in children [5]. These children may have oligospermia or azoospermia but have normal testosterone production and secondary sexual characteristics [9]. The genetic variations in metabolising pathways of drugs like cyclophosphamide could cause variable infertility [10].
2. *Effect of disease* Disease per se can also affect reproductive function. Fever, pain and anorexia are all known to affect semen quality [11]. In Hodgkins lymphoma, 50–70% of men have impaired sperm quality or azoospermia [12]. Dysfunctional sperm may be seen with other lymphomas as well [13]. Up to half of acute leukemia patients may also be azoospermic at diagnosis [14]. Similarly, the fertility rates of oocytes cryopreserved prior to therapy compare less favourably when compared with healthy controls [15].
3. *Effects of chemotherapy* It is important to know the risk of gonadal failure with each chemotherapeutic agent. However, the risks are additive when used in combination. It is more practical to know the risk of gonadal failure according to treatment regimens used in different diseases (Table 2). The risks of permanent infertility are not easy to define [16]. Besides these, there are other agents whose gonadotoxic effects have not been well described. Melphalan in doses used for myeloma autologous HCT is associated with a high risk of gonadal failure. Fludarabine in doses exceeding 320 mg can damage to the spermatozoan DNA [17]. There is insufficient data on the effect of hydroxyurea and rituximab on fertility [18]. Tyrosine kinase inhibitors (TKI) are category D drugs with potential fetal risks. So patients on TKI should also be encouraged for fertility preservation before treatment and conceive while off TKI [19].

Table 2 Risk of gonadal failure as per disease and treatment regimens

High (> 80%)	Low (< 20%)
CY TBI (myeloablative allo-HCT)	CHOP based (non hodgkins lymphoma)
Bu CY (myeloablative allo-HCT)	ABVD (Hodgkins lymphoma)
BEAM (autologous HCT)	7 + 3 regimen (AML)
Cyclophosphamide (> 4 g/m ²)	Multi-agent chemo (ALL)
Testicular/pelvic radiotherapy	Cranial irradiation < 24 Gy
BEACOPP (Hodgkins lymphoma)	TKI (CML)

4. *Effects of radiotherapy* Total Body Irradiation in doses used in myeloablative (> 8 Gy) conditioning regimens for allogeneic hematopoietic stem cell transplantation leads to infertility [20]. Cranial radiation > 35 Gy will lead to permanent infertility through hypogonadotropic hypogonadism [21]. Direct testicular or ovarian radiation > 4 Gy will also lead to infertility [22, 23].
5. *Hematopoietic cell transplantation (HCT)* Few studies have looked at the incidence and outcome of pregnancy after HCT. Long term follow-up of these studies has shown that the incidence of pregnancy is less than 1%. Females (0.4%) are more affected than males (0.9%) [24]. The incidence is worse after TBI containing regimens (1–2%), than BuCY conditioning (4%) or Cy (26%) [25, 26]. The overall conclusion is that fertility rates after HCT cannot be estimated as the denominator population in such cases cannot be known [27].

Modes of Fertility Preservation

Fertility preservation is the preservation of an individual's ability to start a family at the time of his or her choice [28]. The following factors should be considered carefully by the haematologist and the patient prior to planning a particular fertility preservation technique. The counselling of the patient regarding fertility preservation should encompass all these factors and the decision should be left to the patient and his/her partner. Fertility preservation can lead to unrealistic expectations [29].

1. *Infertility rates of the therapy* Therapy which is associated with high rates of infertility warrants a detailed counselling regarding fertility preservation.
2. *Effects of prior chemotherapy or disease per se* Prior therapy or disease itself may have already rendered the patient infertile and fertility preservation procedures may be futile at that point in time.
3. *Safety of the procedure* The fertility preservation technique may potentially delay the start of cancer therapy. Any surgical procedure required for fertility

preservation carries risk in a patient with cytopenia and a compromised immunity.

4. *The risk of gonadal contamination* Hematological malignancies, specifically the leukemias have the tendency to infiltrate the gonads. Any technique involving tissue transplantation has the risk of reintroduction of the disease into a patient.
5. *The unknown effectiveness of the procedure* The data on efficacy of some fertility preservation techniques in oncology patients is limited.
6. *Other factors* Overall prognosis of the disease, financial implications and status of his family should also be considered.
7. *Assisted reproductive techniques (ART)* Fertility preservation is only the first part. For conception ART is needed. The costs and success of ART are very variable [30].

It is important to assess the patient at each stage of therapy for feasibility of fertility preservation. The choice will be based on the age of the patient, marital status and overall health of the patient. It is important to provide all the available information to the patient and guide him in making an informed decision.

Established Options

1. *Semen cryopreservation* Sperm banking through semen cryopreservation is the easiest method of fertility preservation that can be offered to male patients with cancer. It ideally requires 2–7 days of sexual abstinence but may be collected at a short notice if needed. Semen is collected by masturbation, penile vibration, electroejaculation or rarely fine needle aspiration from the testis [31]. Immaturity of the testis and religious issues are some of the barriers to this method of fertility protection.
2. *Cryopreservation of mature oocyte* This technique requires ovarian stimulation, oocytes retrieval and oocyte cryopreservation without fertilisation. This is the only option available for adolescent girls and unmarried women. This option requires a minimum period of 2–3 weeks for the entire process. Cumulative

pregnancy rates post oocyte transfer is more than 50% [32].

3. *Embryo cryopreservation* The technique involves ovarian stimulation, oocyte retrieval and in vitro fertilisation with spermatozoa followed by cryopreservation of the embryo. This is a valid option in married women or women willing for in vitro fertilization from a donor sperm.

Experimental Options

1. *Testicular cryopreservation* The procedure involves surgically harvesting testicular tissue, cryopreserving it and re-implanting at an ectopic site after completion of therapy. It is the only fertility preservation option for pre-pubertal boys.
2. *Ovarian tissue cryopreservation* In this procedure, primordial follicles that contain small, less differentiated oocytes are surgically harvested and cryopreserved. To restore fertility, the tissue is thawed and grafted to allow for growth of follicles and oocyte maturation. This is the only fertility preservation technique available for pre pubertal females.

Both the testicular and ovarian tissue cryopreservation are associated with a theoretical risk of contamination by leukemic stem cells and the risk of reintroduction of the disease in a patient who is in complete remission. A PET-CT scan may be done prior to collection of gonadal tissue as it has a good negative predictive value for lymphomas. The cryopreserved tissue may be analysed for any evidence of disease by molecular techniques after thawing and prior to re-use [33].

3. *In-vitro maturation* This process involves aspiration of immature oocytes and pre-pubertal testicular tissue. The gametes then undergo in vitro maturation for further preservation or use.
4. *Gonadal protection through hormonal suppression* The procedure involves hormonal suppression using Gonadotropin-releasing hormone (GnRH) agonist to induce a block in gametogenesis, This is presumed to protect the gametes from harmful effects of cytotoxic therapy and irradiation. The block is reversed later using hormones and fertility is restored. Animal models have been successful but could not be replicated in humans [34]. A Cochrane meta-analysis demonstrated its efficacy in ovarian protection, although the study could not demonstrate a statistical difference in pregnancy rates [35]. The disadvantages of this technique include the need to start 10 days prior to therapy and the concern that it may interfere with the efficacy of chemotherapy.

Barriers to Fertility Preservation

A survey of physician and patient attitudes and barriers to fertility preservation in the authors hospital (a tertiary referral, premier hospital in North India) (n = 25) revealed the following (Fig. 1). Majority of the physicians skipped the fertility counselling and referral part of their consultations. The common reasons for this were lack of time to discuss, lack of referral facilities, and lack of time for initiating treatment. From the patient's perspective the common reasons for deferring fertility preservation were high costs and cancer first attitude.

Decision for the Hemato-Oncologist

The summary information in Table 3 may help the hemato-oncologist in deciding referral for fertility preservation. It is balance between the probabilities of gonadal failure with chemotherapy, disease cure and success of assisted reproduction techniques (ART). For most patients it is also a balance between the costs of chemotherapy and costs of ART. Fertility preservation and management is a team approach between the hemato-oncologists, endocrinologists, urologists, obstetrician-gynaecologists, infertility experts, psychologists and geneticists. Conscious efforts are needed to bridge the gaps in referral and interdisciplinary team members to ensure haematological malignancy patients get the best beyond their cancer treatment.

Compliance with Ethical Standards

Conflicts of interest The authors have no potential conflicts of interest to disclose.

Ethical Approval This article does not contain any studies with human participants performed by any of the authors.

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Fig. 1 Barriers to fertility preservation**Table 3** Factors to guide decisions in fertility preservation in hematological malignancies

Disease	Probability of gonadal failure %	Costs of chemotherapy ₹	Probability of cure %	Decision to refer before treatment	Probability of ART success	Costs of ART ₹
AML	< 20	10–15 lakhs	50–60	Less likely,	Males 30–70%	Males
ALL	< 20	5 lakhs	40–90	Can't wait to start treatment	Females 10–30%	~ 50,000
HL	< 20	50,000	80	Likely if patient willing		Females ~ 1.5–2 lakhs
NHL	< 20	2 lakhs [®]	60			
Transplant (incl. non-malignant indications)	> 80	5 lakhs (auto) 15 lakhs (allo)		Definitely		

[®] Rituximab, ART assisted reproductive techniques, ₹ Indian national rupees

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