Review

Implications of systemic malignancies on human fertility

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Abstract

Cancer patients have now longer life expectancy due to improved treatment modalities. As the mortality rate decreased and the survival rate increased, the consequences of cancer treatment in terms of impaired fertility became more frequently encountered. The objective of this review is to highlight fertility issues associated with systemic malignancies. Systemic malignancies lead to deterioration of human fertility directly or indirectly as a result of cytotoxic treatment regimens. A variety of measures may be used to decrease the incidence of fertility decline that occurs. Gamete cryopreservation represents a widely accepted method for fertility preservation in cancer patients. In addition, other procedures such as germ cell transplantation and ovarian cryopreservation, which are currently being developed, are expected to make significant contribution in these cases. However, there are some ethical issues that should be considered before offering patients any of these options.

Keywords: cancer, ethical issues, gamete cryopreservation, germ cell transplantation, ovarian cryopreservation

Introduction

Improved treatment regimens for malignant diseases have forced a radical change in the way cancer survivors perceive their disease. In the past, patients tended to be most concerned about survival rates and disease recurrence. Nowadays, patients are also concerned about quality of life issues such as fecundity (Meirov and Nugent, 2001). This is evidently clear in diseases such as breast cancer, leukemia and Hodgkin’s lymphoma, as they tend to affect young patients at reproductive age.

Unfortunately, neoplastic diseases and their treatment commonly impair fertility, either temporarily or permanently leaving many patients unable to bear children. Systemic malignancies impact fertility in many ways. Some of these diseases tend to metastasize in the hypothalamus and pituitary, thus affecting gonadotrophin secretion, resulting in hypogonadism and infertility. In addition, chemotherapy and radiation, both of which are used to treat systemic malignancies, are toxic to the male and female gonads (Agarwal et al., 2004). The main objective of this article is to provide an overview of the close relationship between malignant diseases and human fertility. Specifically, it describes the changes that occur in male and female fertility potential as a result of malignancy and/or its treatment regimens. In addition, it also provides a summary of various options for fertility preservation in cancer patients. Such information would be of importance in counseling patients affected with malignancy while still in the reproductive age group.

Fertility decline associated with systemic malignancies

Infertility associated with malignant disease was considered to be mainly a side effect of the drugs and irradiation used during the course of treatment. However, this view is rapidly changing due to strong evidence that decreased fertility sometimes exists before treatment. In general, malignancy is associated with an increased catabolic state and malnutrition. Therefore, most patients experience weight loss and decreased...
reproductive capacity. In addition, hypothalamic dysfunction can occur and pituitary gonadotrophin levels can fall, which in turn impacts fertility (Vigersky et al., 1977). Stress hormones may further reduce fertility by leading to a rise in prolactin and endogenous opiate secretion, which in turn suppress gonadotropins (Schenker et al., 1992).

Testicular dysfunction and semen abnormalities were reported in males with Hodgkin’s lymphoma prior to the initiation of therapy (Marmor et al., 1986; Fitoussi et al., 2000). In a study conducted on 158 male patients with Hodgkin’s lymphoma (Rueffer et al., 2001), severe damage to fertility was observed in 21% of patients before treatment. The decrease in fertility was most prominent in the patients with an elevated erythrocyte sedimentation rate (ESR) and in those with advanced disease. In another study, semen analysis showed that 70% of patients with Hodgkin’s lymphoma had reduced fertility before therapy regardless of the disease stage or systemic symptoms (Viviani et al., 1991).

An immune-mediated disorder that alters the balance between subpopulations of lymphocytes may be behind the testicular dysfunction associated with Hodgkin’s lymphoma (Barr et al., 1993). Other structural abnormalities in the testicular parenchyma such as tubular hyalinization were also detected in these cases (Chapman et al., 1981). In addition, cytokines (e.g., interleukins and tumour necrosis factor) that are secreted by tumour tissue may be partly responsible for the decline in fertility prior to the initiation of therapy (Marmor et al., 1986).

Effects of malignancy treatment on human gonads

The effects of cancer therapy on testicular architecture vary with the patient’s age and pubertal status. It was initially thought that the testicles of pre- and peri-pubertal males were less vulnerable to toxic effects induced by treatment. However, it is now clear that these patients experience as much testicular structure damage following chemo/radiotherapy as adults (Puscheck et al., 2004).

Although the Sertoli cells usually maintain a protective barrier between the blood and the testicular germ cells, many chemotherapeutic drugs can severely interrupt the integrity of this barrier. Germ cells that do actively differentiate are more susceptible to cytotoxic injury resulting in necrosis. As a result, cytotoxic therapy can deplete germ cells to the point where the seminiferous tubules will only contain Sertoli cells. Some stem cells may survive after cytotoxic insult, but will fail to differentiate into mature spermatozoa for several years (Meistrich et al., 1992).

Unlike male germ cells, female germ cells proliferate only during prenatal life; after birth, they progressively decrease in number due to apoptosis, and ovulation. Germ cells inside the female gonad do not proliferate whereas the somatic cells do. Radiation and chemotherapy induce oocytes to undergo apoptosis, which reduces the number of germ cells (Tilly and Kolesnick, 2002) and results in oestrogen insufficiency. Therefore, when follicles are destroyed by cytotoxic therapy, the frequency of menses decreases and amenorrhoea commonly occurs. Irreversible ovarian failure and menopause occur if the number of follicles falls below that which is required for menstrual cyclicity. The exact incidence of premature ovarian failure (POF) after chemotherapy is difficult to establish because there are many contributing factors. Depending on the type of chemotherapy regimen used, the incidence of amenorrhoea ranges from 0 to 100% (Bines et al., 1996). Temporary amenorrhoea occurs when cytotoxic drugs destroy maturing follicles whereas permanent amenorrhoea or POF occurs when all primordial follicles are destroyed (Warne et al., 1973; Gradishar and Schilsky, 1989).

Effects of malignancy treatment on fertility

The seminiferous epithelium inside the testes is most sensitive to the detrimental effects of chemotherapy (Brougham et al., 2003). Therefore, after treatment with gonadotoxic agents, patients may be rendered oligozoospermic or azoospermic. Because testosterone production by the Leydig cells is usually unaffected, patients still develop normal secondary sexual characteristics (Thomson et al., 2002). However, treatment with high, cumulative doses of gonadotoxic chemotherapy can also lead to Leydig cell dysfunction.

Indeed, Leydig cell dysfunction is not observed until doses of 20 Gy are administered to prepubertal boys and up to 30 Gy in sexually mature males (Shalet et al., 1989). On the other hand, doses as low as 0.1–1.2 Gy can have detectable effects on spermatogenesis in adult men, with doses over 4 Gy causing more permanent effects (Centola et al., 1994).

Long-term female survivors treated with total body irradiation and bone marrow transplantation (BMT) are at risk for ovarian follicular depletion, impaired uterine growth and blood flow in addition to early pregnancy loss and premature labour if pregnancy is achieved (Critchley et al., 2002). During BMT, patients may be given alkylating agents and receive total body irradiation for conditioning, both of which result in POF, hormonal disturbances and eventually, the inability to parent children (Hinterberger-Fischer et al., 1991). Because women who are older than 30 years face a higher incidence of POF following chemotherapy, their treatment regimens should contain fewer alkylating agents (Franchi-Rezgui et al., 2003).

Impact of cancer treatment on the genetic material

Patients undergoing cancer treatment are at risk of transmitting impaired genetic material to their offspring (Meistrich, 1993). In females, most alkylating agents and a variety of other chemotherapeutic drugs induce chromosome aberrations or other mutations in developing oocytes that result in embryonic death (Witt and Bishop, 1996). On the other hand, radiation and several alkylating agents can produce single-gene mutations and chromosomal translocations in spermatogonia (Witt and Bishop, 1996).

The persistence of a mutation depends mainly on its location. Mutations that occur early in stem spermatogonia will produce mutation-carrying sperm for the lifetime of the male whereas those occurring in later stages of development will only be transmitted to half of the female offspring.
spermatogenesis will only lead to a mutation-carrying sperm for a few months. Meiotic and post-meiotic germ cells are more susceptible to mutations than are stem spermatogonia. Therefore, the mutational risks are highest when a pregnancy occurs within one spermatogenic cycle after the male is exposed to the damaging agent (Meistrich, 1993).

Although sperm DNA damage can be assessed with various techniques (Agarwal and Said, 2003), none can definitively determine whether the mutations will be passed onto any offspring. Sperm DNA integrity can vary greatly among cancer patients; however, patients with Hodgkin’s and non-Hodgkin’s diseases generally have a significantly higher prevalence of DNA damage than healthy men (Kobayashi et al., 2001). However, in most instances no major congenital abnormalities can be expected in the offspring of males who received radiation therapy (Hyer et al., 2002).

Fertility following malignancy treatment

Sperm quality may naturally improve after cancer treatment (Fossa et al., 1993; Marmor and Duyck, 1995; Meistrich et al., 1997; Costabile and Sipevak, 1998). However, some defects may persist. The incidence of infertility in men who have recovered sperm production following cytotoxic therapy is generally not higher than that of the general population. Cancer patients with sperm counts below normal (oligozoospermic) are still capable of having children (Marmor and Duyck, 1995). Similarly, infertile women who have menstrual dysfunction following cytotoxic therapy may be treated for menstrual dysfunction and infertility in a manner similar to that of the general population. However, the risk of an adverse pregnancy outcome is higher in these women, and they may require closer observation (Critchley, 1999).

The management of a pregnancy in a woman with a malignant disease may be difficult. Pregnancy itself does not adversely affect the natural course and prognosis of the disease (Griesshammer et al., 1998). However, such women are more likely to experience thrombotic or bleeding complications. Diseases such as chronic myeloid leukaemia (CML) may result in placental insufficiency and increased fetal prematurity and mortality (Miller, 1976). To avoid chemotherapeutic agents during pregnancy, repeated leukapheresis has been recommended as the therapy of choice to control the white blood cell count (Fitzgerald et al., 1986).

Cancer treatment does not seem to affect the outcome results for assisted reproductive techniques. Alkylating agents, which are used extensively in the treatment of breast cancer, lymphomas, and leukaemias, and severe autoimmune disease do not seem to affect the fertilizability of the oocytes (Chen et al., 1998). Although these findings were confirmed in another study (Ginsburg et al., 2001), the number of oocytes obtained in women treated with chemotherapy was somewhat lower due to diminished response to ovulation induction (Ginsburg et al., 2001).

Fertility preservation following malignancy

Semen cryopreservation

Semen cryobanking is a widely available and inexpensive option that yields good results and provides a reasonable chance of establishing pregnancy after cancer therapy (Sanger et al., 1992). Cryopreserving semen after the start of therapy would adversely affect their chromosomal structure, causing de-novo mutations. Therefore, it is crucial to cryopreserve spermatozoa before chemotherapy or radiotherapy and also to advocate the use of contraception during therapy and for 6 months after (Meistrich, 1993;ARSAC, 1998).

Patients diagnosed with cancer used to be considered poor candidates for sperm cryopreservation because they present with disease-induced suboptimal semen quality and cryosensitivity. Men with Hodgkin’s lymphoma have pre-freeze and post-thaw sperm quality that is below normal (Reed et al., 1986; Agarwal and Newton, 1991). However, almost 40% of patients who cryopreserve their semen may be able to achieve a healthy live birth using one of the assisted reproductive techniques (Agarwal et al., 2004). Based on our experience in the last two decades, the percentage decline in semen quality (from pre-freeze to post-thaw) in patients with cancer is similar to that of normal donors. This suggests that the effect of cryodamage on spermatozoa from patients with cancer is similar to that of normal donors (Hallak et al., 1998; Agarwal, 2000).

As a general rule, there is no cancer group for which spermatozoa cannot be retrieved and stored (Bahadur et al., 2002). Even the absence of spermatozoa in semen should not prevent physicians from attempting to preserve a patient’s fertility. In many cancer patients who suffer from azospermia before treatment, testicular sperm extraction (unilateral or bilateral) ‘Onco-tese’ may be successfully attempted, and the retrieved spermatozoa may be cryopreserved for future use (Schrader et al., 2003).

It is of interest to note that only a small percentage of patients (<10%) who bank their spermatozoa before chemotherapy or radiotherapy return for assisted reproduction (Audrins et al., 1999; Schover et al., 1999; Lass et al., 2001). This finding may be explained by several reasons: recovery or waiting for possible resumption of spermatogenesis, short period from original illness, anxiety regarding potential risks for the children, and uncertainty about their long-term health and therefore suitability to be parents (Hallak et al., 1998). However, trends have started to change, and awareness of sperm banking has increased over the past 4–5 years, coinciding with the advent of intracytoplasmic sperm injection (ICSI). Our sperm bank records show a steady increase in the number of patients who bank their spermatozoa and also use it for assisted reproduction after their treatments.

Testicular tissue harvesting

Testicular tissue can be harvested from a biopsy and stored either as a tissue section or as isolated germ cells, before cancer therapy. Following cure, this tissue can be thawed and used to produce offspring in one of two ways: the stored germ
cells can be re-implanted into the patient’s own testes to restore natural fertility, a procedure known as germ cell transplantation, or the stored stem cells can be matured in vitro until they are able to achieve fertilization via ICSI (Brougham et al., 2003). Although these two measures have been the subject of intensive research in the last decade, further refinements in the protocols used may still be needed before they can be used routinely in clinical practice.

It is possible to reinitiate spermatogenesis after transplantation of cryopreserved testicular germ cell suspensions. Although cell survival is acceptable, current protocols still require improvement (Frederickx et al., 2004). Establishing a successful method for testicular stem cell transplantation of frozen–thawed testicular cells would be of immense benefit for many patients undergoing sterilizing treatment, specifically in pre-pubertal boys with childhood cancer, since no active spermatogenesis is present and no sperm cryopreservation will be feasible.

Before stem cell transplantation can be considered for preserving the fertility of pre-pubertal boys, two issues must be carefully examined (Aslam et al., 2000). First, the testis biopsy taken from the cancer patient may contain malignant cells. These cells must be removed from the cell suspension because studies in rats have shown that one single malignant cell can reintroduce the disease. Second, the cell suspension consists of all testicular cells, and the proportion of spermatogonial stem cells is very low (estimated at 1/5000) (Jahnukainen et al., 2001).

The technique of in-vitro maturation of germ cells may be used in adults who received high doses of gonadotoxic drugs/irradiation to the extent that the somatic Sertoli cells become incapable of performing their function of supporting spermatogenesis. In these cases, transplanted germ cells will not have a suitable environment to develop; therefore in-vitro maturation of germ cells may be considered. However, the procedure represents another technical challenge and despite multiple reports and methodologies (Tesarik and Mendoza, 2003), no current protocol can be described as reliable.

Oocyte cryopreservation

The therapeutic role of oocyte freezing for young cancer patients has been generally well received and welcomed (Lockwood, 2003). Although successful fertilization and embryonic cleavage have been reported after injection of cryopreserved thawed oocytes, the pregnancy rate is not high enough to justify its routine use in clinical practice (Gook et al., 1994). The main reason for poor outcomes after oocyte cryopreservation is related to the oocyte’s structural complexity. Nevertheless, recent technical modification such as changes in the freezing protocol greatly improved the clinical efficiency of oocyte cryopreservation (Porcu, 2001). Preliminary reports from 18 patients suffering from various malignancies suggest that oocyte storage may be an alternative pragmatic option for fertility preservation, as the duration of oocyte storage did not interfere with its survival and pregnancies occurred even after several years of gamete cryopreservation (Porcu et al., 2004). However, the presence of other factors such as uterine impairment would be of major concern. In addition, complications during pregnancy and pre-term deliveries will be expected in these cases (Larsen et al., 2000).

Ovarian tissue cryopreservation

Ovarian tissue banking in humans is being considered to restore fertility in patients who lose ovarian function because of chemotherapy or radiotherapy (Gosden, 2002). Ovarian tissue cryopreservation and transplantation first emerged in rodent studies and then in sheep and human ovarian xenograft studies (Oktay, 2001). Although promising, there is a theoretical risk that malignant stem cells will be re-implanted along with the thawed cryopreserved ovary (Kim et al., 2001; Blumenfeld et al., 2002). Ovarian tissue cryopreservation is currently under evaluation and is not offered as a routine service. However, a live birth has been recently reported following the autotransplantation of cryopreserved ovarian tissue (Donnez et al., 2004). This report offers promising information that may advocate the use of ovarian tissue cryopreservation from patients before cancer treatment.

Choice of cytotoxic regimens

Currently, treatment regimens for systemic malignancy include a variety of chemotherapeutic agents, all of which affect reproductive functions differently. For young patients, it is important to select an agent with minimal toxicity but maximal therapeutic effect. For example, NOVP (mitoxantrone, vincristine, vinblastine, prednisone) may be preferred over MOPP (mustine, vincristine, procarbazine and prednisone) for the treatment of diseases such as Hodgkin’s lymphoma. Although NOVP markedly affects spermatogenesis, sperm production recovers rapidly after treatment, usually within 3–4 months. This rapid recovery is due to the fact that NOVP chemotherapy damages spermatogenic germ cells rather than inhibiting stem cells (Meistrich et al., 1997).

Similarly, ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) is used to treat Hodgkin’s disease instead of MOPP because the former dramatically reduces gonadal toxicity (Viviani et al., 1985). VAPEC-B (doxorubicin, cyclophosphamide, etoposide, vincristine, bleomycin and prednisolone), which is used in the treatment of non-Hodgkin’s lymphoma, minimizes the dose of cyclophosphamide and therefore results in less gonadal failure than CHOP-Bleo (cyclophosphamide, vincristine, prednisone, bleomycin) (Radford et al., 1994).

Gonadal shielding

The gonads must be outside the field of radiation or shielded from the direct radiation beam unless they are being irradiated directly as a result of actual or potential neoplastic involvement. Although gonadal shields can reduce the amount of radiation 2- to 5-fold, some radiation may still reach the gonads. For example, the gonads typically receive 2–3 Gy with an inverted Y-field, which is used for Hodgkin’s disease (Bieri et al., 1999). To minimize ovarian exposure, oophoropexy may be performed to relocate the ovaries away from the direct beam (Sy Ortin et al., 1990; Morice et al., 2000). Laparoscopic oophoropexy may be of benefit in cases of Hodgkin’s disease if performed before pelvic irradiation (Williams et al., 1999).
Medical treatment

Testosterone suppressors such as gonadal steroids, gonadotropin-releasing hormone (GnRH) analogues and anti-androgens when used before and during cytotoxic therapy in male rats can enhance the recovery of spermatogenesis and fertility (Meistrich and Shetty, 2003). It was assumed that recovery of stem spermatagonia cells could possibly be stimulated after prolonged periods of iatrogenic azoosperma, but research does not necessarily support that theory. Hormone treatment given before and during cytotoxic therapy was found to protect spermatogenesis in only one of eight clinical trials (Masala et al., 1997).

GnRH agonists may protect ovarian function from the effects of cyclophosphamide (Ataya et al., 1995) by decreasing the recruitment of primordial follicles. Strong evidence supports the use GnRH agonistic analogue to minimize the gonadotoxiceffect of chemotherapy because it induces pre-pubertal milieu (Blumenfeld 2002; Blumenfeld et al., 2002). However, the feasibility of using oral contraceptives or GnRH agonists to protect women against ovarian damage has not been established (Waxman et al., 1987).

Hormone replacement therapy (HRT) should be considered in young pre-menopausal women who have developed ovarian failure due to malignancy or cancer treatment (Mulder, 1999). Even with the use of HRT, though, uterine size can still decrease by 40% (Critchley et al., 2002). Finally, it is important to mention that any residual ovarian function remaining after chemotherapy is considered a good prognostic sign because it may be stimulated with steroid hormones and/or gonadotropins (Chatterjee and Goldstone, 1996).

Oocytes exposed to chemotherapeutic agents in vitro undergo various changes leading to apoptosis (Tilly, 1998). Sphingosine-1-phosphate may be an example of an apoptotic inhibitor. The oocytes of mice that had been treated with sphingosine-1-phosphate therapy resisted apoptosis that was induced by doxorubicin (Morita et al., 2000). The concept offers a promising experimental alternative to guard against apoptosis. With the eventual identification of the molecular and genetic framework of chemotherapy-induced germ cell death, apoptotic inhibitors may some day play a role in preventing oocyte loss.

Ethics of fertility preservation

Options for future fertility following cancer treatment must be considered in the patient’s best interests. Thus, the advantages of any intervention or of an active decision not to intervene must outweigh any disadvantages, both in the short and long term. Any intervention intended to preserve fertility must have a sound evidence base as well as moral provenance. It should neither raise unrealistic expectations nor have long-term adverse effects on the patient or their offspring (Grundy et al., 2001).

A competent person must give informed consent voluntarily. However, in view of the complexity of the issues surrounding fertility preservation, the anxieties of both patients and their families at the time of diagnosis and the limited time for discussion due to the urgency of commencing treatment, the validity of such consent may be impaired. The first stage of consent is for the collection and storage of the germinal tissue or gametes. The second stage is for use of the collected material for fertilization.

In addition, it is important to consider what will happen to stored cells in the event of divorce or the patient’s death. While some would advocate destruction of the tissue in the latter situation, others have suggested allowing the parents to allow the tissue to be used for research purposes (Wallace and Walker, 2001). Procedures such as embryo cryopreservation have always generated legal conflicts. The disputes regarding ownership and rights of access to frozen embryos created in relationships that have ended, provide further evidence for the desirability of separating the preservation of fertility potential from the creation of embryos (Lockwood, 2003). Proper regulations and accurate definitions are still needed to govern the new opportunities for preservation of fertility potential for cancer patients receiving damaging treatment regimens (Bahadur et al., 2001).

Conclusions

Today between 50 and 60% of all cancer patients survive for more than 5 years (Fossa, 2004). Many systemic malignancies such as Hodgkin’s lymphoma and breast cancer affect predominantly young patients in the reproductive age group. The decreasing mortality rate and the increasing survival rate as result of effective treatment have made fertility issues more frequently encountered. Patients with systemic malignancies have impaired fertility as a direct effect of the disease or indirectly as a result of the mandatory cytotoxic treatment regimen. The deterioration in fertility potential may be temporary or permanent.

A variety of measures may be used to minimize the deleterious effects of malignancy and its treatment on the human fertility potential. Moreover, assisted reproductive techniques in combination with rapidly evolving understanding of cryobiology currently offer encouraging measures to preserve fecundity following malignancy treatment. These measures should be considered in young adults, and patients should be counselled regarding the pros and cons of each of the available options for fertility preservation.

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