commentaries

Is Fertility Preservation Feasible and Safe With Neoadjuvant Therapy for Breast Cancer?

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INTRODUCTION

Many women of reproductive age who are newly diagnosed with cancer have not yet started their families, whereas others have not completed their families.[1] Previously, the majority of these women would remain childless.[2] Although spontaneous pregnancy is sometimes possible after treatment, fertility potential in the majority of these women will decline as a result of the gonadotoxic nature of some of the most effective chemotherapeutic agents, first and foremost alkylating agents.[3] The immediate, long-term effect is, almost uniformly, diminished ovarian reserve, and in many cases, premature ovarian insufficiency (characterized by amenorrhea or oligomenorrhea in combination with low estradiol levels and high gonadotropin levels).[3-7] With recent advances in assisted reproductive technology (ART), women newly diagnosed with cancer increasingly are pursuing fertility preservation (FP) before chemotherapy or radiation. These patients pursue controlled ovarian stimulation with gonadotropins to produce mature oocytes, which are surgically removed. Subsequently, oocytes can be frozen (through vitrification) if the patient does not have a partner. Alternatively, oocytes may be fertilized with a partner's sperm and the resulting embryos (usually day 5 or day 6 blastocysts) vitrified. These frozen oocytes or embryos can be thawed and used to affect a pregnancy in cancer survivors after clearance by their oncologists to conceive.

Breast cancer is the most common diagnosis among women referred to oncofertility programs[8,9] for two reasons. First, breast cancer is the most common cancer in reproductive-age women,[10] and second, the gold standard treatment has been surgery followed by chemotherapy, which provides oncofertility specialists a window of opportunity (approximately 6 weeks) between surgery and adjuvant therapy. This interval allows ample time for preparation of the patient, including the scheduling of ovarian stimulation according to the patient's cycle and, in some instances, even in managing to complete two FP cycles.[11,12]

Neoadjuvant therapy (NAT) flips the order of treatment, where the oncologist recommends chemotherapy before surgery. Breast cancer treatment is one example of a growing shift from surgery first to NAT.[13,14] The National Comprehensive Cancer Network has outlined clinical scenarios in which NAT is the preferred approach.[15] Previous studies indicated that NAT candidates referred for FP are more reluctant to undergo FP, and many of them will have a consultation with a fertility specialist but never return.[9] Among reasons that have influenced patients' decisions not to pursue FP are concerns with the cost of the procedure (medications usually are donated) and the fear that FP will delay their cancer treatment.

For women diagnosed with breast cancer where NAT is preferred, under what circumstances is a referral for FP appropriate and indicated? Does NAT obligate a shift in priorities? How can we manage to allow as many women as possible to undergo FP without compromising cancer care? We address the medical as well as the emotional aspects of these dilemmas. Although these issues are considered in the context of breast cancer, the most common type of cancer presenting to oncofertility centers, NAT treatment increasingly is used across a wide spectrum of cancer types. As a result, the discussion is relevant to any reproductive-age female diagnosed with cancer when the treatment plan includes NAT.

Recent Advances in FP Management

Advances in ART have made FP a more viable option for patients with cancer. One of the main concerns of oncologists and oncologic surgeons is that FP might have a deleterious effect on tumor progression as a result of ovarian stimulation, especially if treatment is delayed. In particular, estrogen-dependent tumors theoretically could grow and progress as serum estradiol levels rise with gonadotropin treatment. However, stimulation protocols that add letrozole, an aromatase inhibitor, have been successfully implemented and keep serum estradiol close to physiologic levels during the cycle. Limited data on survival and recurrence rates have been reassuring.[16]

A specific concern for NAT is whether the delay in treatment of FP stimulation could have a negative effect on the ultimate outcome. Although in the past we would have started the drugs early in the follicular phase (at the beginning of the cycle), newer protocols enable us to start patients at any point, including the luteal phase (random start).[17] This approach allows physicians to start fertility drugs as early as the same

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day of the initial consultation at the oncofertility center, which thus eliminates the need to wait for the start of a new menstrual cycle. A recent study has shown that use of a random start stimulation protocol in FP patients who undergo NAT does not delay treatment.[18] Thus, even if the treatment plan is chemotherapy in the immediate future, FP is still a possibility, with a cycle completed within 2 weeks.

Because the widespread use of FP is relatively recent, well-designed long-term studies that investigate the outcomes of the various stimulation protocols and subsequent oncology treatments are required to erase doubt that FP does not have a deleterious effect on long-term survival. However, given the known natural history of breast cancer, the start of a short treatment with gonadotropins at any point during the menstrual cycle, with estradiol levels curtailed by letrozole, should not have untoward long-term effects on the patient's prognosis.

Another technological advance in ART that has supported growing FP referrals is the improved pregnancy outcomes of both embryo and oocyte cryopreservation as a result of the shift to vitrification. Oocyte vitrification has been a game changer that results in higher postcryopreservation survival and fertilization rates and elevates viable pregnancy rates to those of fresh oocytes.[19-22] The American Society for Reproductive Medicine has deemed oocyte cryopreservation to no longer be experimental, and it is now routinely used in fertility centers for nonmedical reasons.[23] Cryopreservation of embryos has had long-term follow-up, with viable pregnancies documented in the literature up to 18 years after freezing.[24] Although such long-term data on oocyte cryopreservation are lacking, what is known so far is that the viability of thawed oocytes up to at least 5 years is unchanged.[25-27] Hopefully, longer follow-up studies in the near future will prove similar stability in pregnancy rates as shown for frozen embryos. These advances have dramatically cleared the formerly bleak fertility horizons of women who are single or with an uncommitted partner.

Discovery of a mutated cancer gene introduces additional concerns to the already manifold conundrum the patient experiences. Now the patient worries that her children might inherit her cancer gene mutation. Genetic testing panels for inherited cancer can identify genetic mutations that significantly increase the risk for developing cancer. The most commonly diagnosed mutations in patients with breast cancer are found in *BRCA1* and *BRCA2*, which are present in 10% of patients < 40 years of age.[28-30] By using preimplantation genetic diagnosis (PGD), a biopsy of cells from the blastocyst (day 5 embryo) can be done to analyze DNA for the cancer gene mutation, which allows future transfer of an unaffected embryo and prevention of inheritance of the mutation by the offspring. Although this process can take several weeks to complete, PGD is possible for patients who undergo either adjuvant therapy or NAT.

Given the advances in reproductive technology that make FP safer and more efficient, oncology teams, including physicians and nurses, increasingly are more aware of FP as a viable option that does not negatively affect treatment outcome.[31] FP is truly a multidisciplinary treatment that requires a team-based approach among oncofertility, medical oncology, and surgery, with the patient's health given the highest priority followed by the secondary priority of her fertility future.

Perspectives of Patient Counseling

An additional element to the decision of whether to pursue FP before NAT is the patient's emotional terrain: the NAT scare factor. The decision to treat with chemotherapy first may indicate to the patient that her disease is more serious and that any delay in treatment may jeopardize her chances to survive the cancer. The patient may believe that she has to choose between fertility and survival because in her mind, she cannot have both. However, the focus on survival may lead to regret after treatment of not looking beyond survival to secure the potential for parenthood. Although the threat of losing fertility compounds the already overwhelming barrage of bad news, studies have shown that when the patient is aware that she can still become a mother after surviving cancer, the prospect of having children in the future gives her hope and boosts her morale.[32]

The key to managing FP without compromising or delaying care is prompt referral to oncofertility. One study found that the mean interval between diagnosis and presentation to the FP office is 18 days.[33] This interval is too long and frequently is associated with soaring anxiety in the patient, which often prompts the patient to reject FP for fear that additional delay in treatment will negatively affect her chances for cancer survival. In fact, recent studies have shown no delay in NAT in patients who elect to go through FP compared with those who do not.[18,34] In addition, no difference was found in survival rates between patients who initiate NAT 4 weeks, 4 to 8 weeks, or > 8 weeks after diagnosis, including those with the worst prognosis (ie, triple-negative breast cancer).[18] Thus, with prompt referral, FP is possible and safe in patients with breast cancer who undergo NAT.

CONCLUSION

The steady rise in the number of patients treated with NAT demands a closer look at how FP relates to the cancer treatment. That this regimen is considered to have better results with higher survival rates highlights the need to provide the patient with realistic fertility prospects after aggressive treatment that is likely to induce permanent damage to her ovaries. Advances in ART enable patients to bank eggs and embryos with a high level of confidence that they will have excellent chances to conceive after they complete treatment and are disease free. In cases where a cancer gene mutation is identified, PGD allows us to shield the next generation from inheriting it. FP is possible with NAT and will not significantly delay treatment if the referral is made promptly after diagnosis. We urge oncologists and all other team members to discuss the

effect of treatment on fertility and FP options at the time of their initial consult, as suggested by ASCO and American Society for Reproductive Medicine guidelines.[35,36] Oncofertility physicians understand the urgency to meet with and treat patients with cancer as soon as a diagnosis and treatment plan have been made. Patients are added to the schedule promptly, typically with 48 hours, to avoid additional delay in their potential FP cycle.

The patient is still in a state of shock when newly diagnosed with cancer. As we help her to process the new reality, most of the time we can reassure her that her chances for long-term survival are high. Most patients referred for FP have a good prognosis,[8,9] such as breast cancer (stage I and stage II 5-year survival rates, 98.9% and 85.2%, respectively) and Hodgkin lymphoma (stage I and stage II 5-year survival rates, 92.2% and 93.1%, respectively).[37] While the patient tries to compartmentalize the ramifications of her disease, oncologists and fertility providers alike should emphasize that survival and fertility are not mutually exclusive. The patient can survive her cancer and have a family. Motherhood after cancer survival ushers in a new dawn.

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