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Assessing and minimizing reproductive risks of cancer chemotherapy

NOW THAT MORE AND MORE CHILDREN and young adults are surviving malignant diseases such as acute leukemia, osteogenic sarcoma, Hodgkin's disease, non-Hodgkin's lymphomas, and germ cell tumors, a new problem is arising: the often-intensive chemotherapy necessary to cure the disease can also affect the patients' ability to have children, and sometimes causes birth defects in the children the patients do have.

An important concern about chemotherapy in young patients is the risk of sterility or birth defects

EFFECTS OF CHEMOTHERAPY ON MALE GONADAL FUNCTION

Most male patients who receive alkylating agents such as nitrogen mustard or cyclophosphamide develop testicular atrophy and azoospermia, even when these drugs are used alone, but spermatogenesis commonly returns several years after therapy is completed if only one alkylating agent was used. For example, in one series of 26 men who developed azoospermia after receiving cyclophosphamide, normal sperm production eventually returned in 12 (46%).

With combination chemotherapy regimens, it is hard to predict the effect on reproductive function of any of the individual drugs used. However, knowing the potential effects of the individual drugs used in treating Hodgkin's disease, researchers predicted that one commonly used regimen, ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), should cause less gonadal dysfunction than another standard regimen, MOPP (nitrogen mustard, vincristine, procarbazine, prednisone). Subsequent clinical data confirmed this hypothesis. In fact, there is relatively strong evidence that the gonadal damage that the MOPP regimen causes is frequently irreversible. The less-toxic effect of the ABVD regimen is one of several factors that should be considered when selecting a chemotherapy regimen in Hodgkin's disease.

Similar data are available in male germ cell tumors, in which one common regimen (cisplatin, etoposide, bleomycin) produces a high incidence of azoospermia. However, most men treated with this regimen gradually recover gonadal function over several years.

Of interest and clinical relevance, the testes appear to be more resistant to cytotoxic chemotherapy before puberty than afterward. Although the intensive chemotherapy often given for diseases such as acute leukemia that occur in prepubescent males can damage the testes, most boys appear to develop normally and few require hormone replacement therapy.

EFFECT OF CHEMOTHERAPY ON FEMALE GONADAL FUNCTION

Like the testes, the ovaries are particularly sensitive to alkylating agents, and are more resistant before puberty than afterward.

Combination chemotherapy regimens cause a high rate of amenorrhea, which in

younger patients appears to be temporary. However, for women older than 25 years, the incidence of permanent amenorrhea and premature menopause (with symptoms of hot flashes and vaginal dryness) is considerably higher. In contrast, prepubertal girls appear to be protected from the effects of cytotoxic chemotherapy (as observed with boys).

TERATOGENIC POTENTIAL OF CHEMOTHERAPY

Experiments in animals and experience in humans have demonstrated that certain chemotherapeutic agents can cause defects in the fetus. Unfortunately, experiments in animals do not always predict the risk of teratogenesis in humans, because animals and humans are different in their susceptibility to the various toxic effects of cancer chemotherapeutic agents.

Decreased spermatogenesis and amenorrhea are common but frequently reversible, particularly in adolescents

The risks to the fetus include:

- Spontaneous abortions.
- Severe developmental abnormalities.
- Premature birth.
- Damage to the cells of the developing liver, lungs, heart, and kidneys.
- Sterility.
- Delayed physical and mental development.
- Mutagenic events leading to cancer later in life.
- Teratogenic events leading to malformations in a subsequent generation.

Granted, most of these concerns are entirely theoretical. However, even if a baby appears normal at birth, considerable time must pass before one can feel comfortable in stating that chemotherapy has not resulted in major clinical problems.

Drugs with teratogenic potential

Alkylating agents (eg, busulfan, chlorambucil, cyclophosphamide) produce a high rate of gonadal dysfunction, but are probably less teratogenic than the folic acid antagonists.

Other drugs known for their teratogenic potential include other antimetabolites (eg, cytarabine, 5-fluorouracil), vinblastine, and procarbazine.

Recommendations

In general, cytotoxic chemotherapy should be avoided if possible during the first trimester of pregnancy, when the developing fetus is most vulnerable. Particularly to be avoided during this time are folic acid antagonists such as methotrexate. During the second and third trimesters the risk of a major developmental abnormality is significantly less.

OPTIMIZING THE CHANCES FOR CHILDBEARING

Sperm cryopreservation is a very reasonable strategy for male patients who will be undergoing chemotherapy. Unfortunately, many cancer patients have low sperm counts or poor sperm motility, making their sperm inadequate for cryopreservation.

The likely reason for the poor sperm quality is that any chronic illness tends to suppress spermatogenesis. Another explanation is that the cancer itself either directly or indirectly inhibits spermatogenesis. For men with poor sperm motility, a reasonable option is in vitro fertilization.

Oral contraceptives have been given to young women during chemotherapy in an effort to prevent gonadal failure by suppressing ovarian function, making the ovaries less susceptible to the effects of the cytotoxic agents. While this is an interesting and reasonable strategy, its effectiveness has not been clearly established.

Gonadotropin-releasing hormones also suppress ovarian function, and might therefore be used to protect the ovaries during chemotherapy. In experiments in animals, these agents prevented ovarian failure during treatment with alkylating agents. As with oral contraceptives, the clinical utility of this approach remains to be critically defined.

Embryo cryopreservation and ovarian cryopreservation may be considered in carefully selected patients scheduled to receive cytotoxic chemotherapy. Again, in this clinical setting, the effectiveness of these interventions is uncertain.

Counseling is critically important for patients and their families. Topics that should be discussed include:

- The relative risks of infertility associated with treatment of the cancer.
- Options for alternative therapeutic strategies (eg, drugs with lower theoretical risk of causing sterility).
- Potential methods to preserve fertility.

SUGGESTED READING

Averette HE, Boike GM, Jarrell MA. Effects of cancer chemotherapy on gonadal function and reproductive capacity. CA Cancer J Clin 1990; 40:199–209.

Doll DC, Ringenberg QS, Yarbro JW. Antineoplastic agents and pregnancy. Semin Oncol 1989; 16:337–346.

Drasga RE, Einhorn LH, Williams SD, Patel SN, Stevens EE. Fertility after chemotherapy for testicular cancer. J Clin Oncol 1983; 1:179–183.

Garber JE. Long-term follow-up of children exposed in utero to antineoplastic agents. Semin Oncol 1989; 16:437–444.

Gradishar WJ, Schilsky RL. Ovarian function following radiation and chemotherapy for cancer. Semin Oncol 1989; 16:425–436.

Heikens J, Behrendt H, Adriaanse R, Berghout A. Irreversible gonadal damage in male survivors of pediatric Hodgkin's disease. Cancer 1996; 78:2020–2024.

Meistrich ML, Chawla SP, Da Cunha MF, et al. Recovery of sperm production after chemotherapy for osteosarcoma. Cancer 1989; 63:2115–2123.

Ortin TT, Shostak CA, Donaldson SS. Gonadal status and reproductive function following treatment for Hodgkin's disease in childhood: the Stanford experience. Int J Radiat Oncol Biol Phys 1990; 19:873–880.

Redman JR, Bajorunas DR, Goldstein MC, et al. Semen cryopreservation and artificial insemination for Hodgkin's disease. J Clin Oncol 1987; 5:233–238.

Rivkees SA, Crawford JD. The relationship of gonadal activity and chemotherapy-induced gonadal damage. JAMA 1988; 259:2123–2125.

Schilsky RL, Sherins RJ, Hubbard SM, Wesley MN, Young RC, DeVita VT. Long-term follow-up of ovarian function in women treated with MOPP chemotherapy for Hodgkin's disease. Am J Med 1981; 71:552–556.

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