Infertility in Patients With Testicular Cancer: Testis, Tumor, or Treatment?

Richard L. Schilsky

The adult testis functions as both an exocrine and an endocrine gland producing spermatozoa and testosterone. Spermatogenesis is a dynamic and complex process divided into three phases: (a) proliferation of spermatogonia to produce spermatocytes and to renew the germ cell pool, (b) meiotic division of spermatocytes to reduce by half the chromosome number in the germ cells, and (c) maturation of the spermatids to become mature spermatozoa (1). Although this process is under the control of pituitary gonadotropins, it is sensitive to many influences including fever, systemic illness, and drugs. Neoplastic disease and its treatment can potentially affect sperm production in a number of ways: (a) a specific cell type within the germinal epithelium might be selectively damaged or destroyed; (b) the proliferative and meiotic phases of spermatogenesis might proceed normally, but sperm maturation might be abnormal, leading to functionally incompetent spermatozoa; or (c) Sertoli cells, Leydig cells, or other supportive or nutritive constituents of the testis might be damaged, resulting in alterations in the particular microenvironment necessary for germ cell production.

Many patients with Hodgkin's disease and testicular cancer are severely oligospermic or azoospermic before treatment is initiated (2-5); however, the cause and natural history of impaired sperm production have not been clearly delineated. Pretreatment testicular biopsy specimens from oligospermic patients with Hodgkin's disease have demonstrated a continuum of abnormalities, ranging from focal maturation arrest and basement membrane thickening to widespread sclerosis of the seminiferous tubules and degeneration of the germinal epithelium (2). These findings are presumed to be directly related to the presence of active Hodgkin's disease because many patients have a history of normal sexual function and fertility prior to diagnosis of Hodgkin's disease and recover normal testicular function following radiotherapy for early-stage disease (6). Impaired sperm production in patients with Hodgkin's disease does not correlate with age, stage of disease, presence of systemic symptoms, or fever. However, a strong inverse relationship has been noted between the presence of sperm agglutinins in serum and sperm concentration, suggesting that oligospermia can, at least in part, be immunologically mediated (4). Other studies of patients with untreated Hodgkin's disease have revealed abnormalities in the hypothalamic-pituitary-testicular axis that may also contribute to suppression of spermatogenesis (3).

The great majority of patients with testicular cancer also have diminished sperm production before therapy is initiated. Biopsy of the contralateral, non-tumor-bearing testis in such individuals has demonstrated significant abnormalities, including hyalinized tubules, spermatogenic arrest, absence of germinal epithelium, and carcinoma in situ (7). Such findings have led to the speculation that a common genetic or environmental factor is responsible for both impaired spermatogenesis and the development of germ cell tumors of the testis. The report by Hansen et al. in this issue (8) provides support for this hypothesis. Patients with stage I testicular cancer treated by orchiectomy alone demonstrated persistently low, indeed declining, sperm production during a median follow-up period of 2.9 years. At the time of orchiectomy, 13 of 21 stage I patients had total sperm counts below the normal value of 80 million. Persistent oligospermia was demonstrated in nine of these patients during the period of follow-up.

In a similar study of 17 patients with stage I testis cancer, Nijman et al. (9) observed an overall improvement in sperm counts 1 year after orchiectomy. This finding suggested that the primary tumor exerted an inhibitory effect on spermatogenesis. However, of 10 patients who were oligospermic prior to orchiectomy, two became azoospermic, three were persistently oligospermic, and only five recovered normal sperm production following orchiectomy, again demonstrating that at least some patients with testicular cancer may have an underlying and an apparently irreversible defect in germ cell production.

In recent years much has been written about the gonadal toxicity of cancer chemotherapy. Clearly, our ability to draw firm conclusions about the effects of any chemotherapy regimen on the testis depends, in part, on our understanding of the effects of the underlying disease on gonadal function. There is little doubt that MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) chemotherapy is severely toxic to the testis, producing permanent infertility in more than 90% of treated individuals (10). In contrast, ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy produces little toxicity to the germinal epithelium; therefore, its use might result in improved fertility by eliminating the suppressive effects of active Hodgkin's disease on spermatogenesis. Hansen et al. (8) and others (11-13) clearly demonstrated that chemotherapy with six cycles of cisplatin, vinblastine, and bleomycin (PVB) causes severe oligospermia or azoospermia in at least 70% of patients undergoing treatment of testicular cancer. Following treatment, spermatogenesis resumes in most patients within

Received June 15, 1989; accepted June 15, 1989.

Section of Hematology-Oncology, University of Chicago Medical Center,
5841 S. Maryland Ave., Box 420, Chicago, IL 60637.
5 years, although a return to normal sperm counts is uncommon. In the study by Hansen et al., sperm production in chemotherapy-treated patients was similar to that in untreated patients by 1.5 years after completion of chemotherapy. This finding suggests that the effects of PVB on the testis are rapidly reversible but that oligospermia may, nevertheless, persist as a result of underlying abnormalities in germ cell production.

Infertility in male patients with cancer appears to be multifactorial in origin. At diagnosis, many patients may be oligospermatic as a result of a suppressive effect of the primary tumor on spermatogenesis. If the treatment employed does not itself destroy the germinal epithelium, then fertility might actually improve after chemotherapy as the inhibitory effects of the primary tumor disappear. Persistent gonadal dysfunction following treatment may not always be attributable entirely to chemotherapy. Rather, it may reflect an underlying defect in germ cell production such as that which appears to be present in many patients with testicular carcinoma. Thus, careful pretreatment evaluation and long-term follow-up are necessary to define clearly the impact of the disease and its treatment on fertility. The follow-up of the patients with stage I disease by Hansen et al. will continue to provide important insights into the natural history of testicular dysfunction in patients with germ cell tumors. In addition, it may help to define the risk of second primary tumors arising in the potentially abnormal residual germinal epithelium.

References