Outcome and Reproductive Function After Chemotherapy for Ovarian Dysgerminoma

By Molly Brewer, David M. Gershenson, Cynthia E. Herzog, Michele Follen Mitchell, Elvio G. Silva, and J. Taylor Wharton

Purpose: **To review the outcome for all patients with ovarian dysgerminoma treated at the M.D. Anderson Cancer Center who received bleomycin, etoposide, and cisplatin (BEP) and to assess the menstrual and reproductive function of those who received conservative treatment.**

Patients and Methods: **Clinical information was abstracted from the medical record. Patients completed a detailed questionnaire about menstrual and reproductive function; those who did not return the questionnaire were interviewed by telephone.**

Results: **Twenty-six patients were identified as having been treated with BEP chemotherapy for pure ovarian dysgerminoma from January 1984 to January 1998. Their median age was 19.5 years (range, 7 to 32 years). Sixteen patients underwent fertility-sparing surgery in the form of unilateral salpingo-oophorectomy. At a median follow-up time of 89 months, 25 (96%) of the 26 patients remained continuously disease-free. One patient apparently developed a second primary dysgerminoma in her remaining ovary after BEP and was clinically disease-free after further treatment. Of the 16 patients who underwent fertility-sparing surgery, one was lost to follow-up when she was pregnant, and one was still premenarchal. Of the remaining 14 patients, 10 (71%) maintained their normal menstrual function during and after chemotherapy, and 13 (93%) had returned to their prechemotherapy menstrual pattern at the time of the questionnaire. Five pregnancies have occurred thus far, and two patients have had difficulty conceiving.**

Conclusion: **Most patients with metastatic dysgerminoma can expect cure with maintenance of normal reproductive function when treated with conservative surgery and BEP chemotherapy.**

J Clin Oncol 17:2670-2675.

ALTHOUGH RELATIVELY uncommon, dysgerminoma is the most common malignant germ cell tumor of the ovary, accounting for approximately 2% of all ovarian malignancies. It arises from primordial germ cells and occurs predominantly in girls and young women. It represents the female counterpart of testicular seminoma and is unique among malignant ovarian germ cell tumors for its bilaterality and exquisite radiosensitivity.

For several decades, radiation therapy was the traditional postoperative treatment for patients with metastatic dysgerminoma.[1,2] Although the cure rate with such treatment was excellent, irradiation usually produced ovarian failure. In 1984, we began to treat patients with metastatic dysgerminoma with the chemotherapy combination of bleomycin, etoposide, and cisplatin (BEP) in an effort to achieve equal efficacy to that of radiotherapy while preserving fertility in these young and often nulligravid girls and women. At that time, there was a growing body of literature on the chemosensitivity of metastatic testicular seminoma[3-6] and scattered reports documenting the sensitivity of dysgerminoma to chemotherapy.[7-11] We initially reported sustained remissions in two patients[12] and subsequently found that all 14 of our patients with dysgerminoma (nine with advanced or recurrent disease) were disease-free after treatment with BEP.[13] Other investigators also have reported their experience with platinum-based combination chemotherapy for ovarian dysgerminoma.[14,15]

The purpose of the present study was to review retrospectively the outcome for all patients with ovarian dysgerminoma treated at The University of Texas M.D. Anderson Cancer Center with BEP chemotherapy and to assess the menstrual and reproductive function of those who received conservative treatment.

PATIENTS AND METHODS

Twenty-six patients with ovarian dysgerminoma who had been evaluated at the M.D. Anderson Cancer Center and treated with BEP chemotherapy in the period from January 1984 to January 1998 were identified. All patients underwent initial surgery. For patients who underwent surgery at M.D. Anderson, residual disease was documented carefully in terms of size and extent. For patients who underwent surgery elsewhere, residual disease was documented by review of the dictated operative summary and discussion with the operating surgeon. This information was supplemented with data from physical examination and appropriate imaging studies.

Histologic review was performed by gynecologic pathologists of the Department of Pathology. Tumors were classified as dysgerminoma according to the World Health Organization criteria.[16] Only cases of

From the Departments of Gynecologic Oncology, Pediatrics, and Pathology, The University of Texas M.D. Anderson Cancer Center, Houston, TX.

Submitted January 4, 1999; accepted April 23, 1999.

Address reprint requests to David M. Gershenson, MD, Department of Gynecologic Oncology, Box 67, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030; email dgershen@mdanderson.org.

0732-183X/99/1709-2670

pure dysgerminoma were included in this study; cases of other histologic types of malignant ovarian germ cell tumors, including mixed germ cell tumor with a dysgerminoma component, were excluded. Tumors were staged according to the International Federation of Gynecology and Obstetrics classification system.

All patients received postoperative BEP chemotherapy. The dosages and schedules varied somewhat. Most patients received a regimen consisting of bleomycin 10 to 15 mg daily on days 1 through 3 by continuous intravenous (IV) infusion, etoposide 100 mg/m^2 IV daily on days 1 through 3, and cisplatin 100 mg/m^2 IV on day 1. The lower bleomycin dose was selected for pediatric patients and smaller adult patients. Cisplatin was mixed in 1 L normal saline or 0.5 L normal saline with 50 g mannitol and delivered IV over 4 hours. This regimen was repeated at 4-week intervals for a planned total of three to six cycles. The number of cycles depended on several factors, including the objective response of any measurable tumor, the patient's tolerance of chemotherapy, and the preferences of the attending physician.

Before each course of chemotherapy, patients underwent a complete blood count, platelet count, chemical survey, and serum tumor marker studies as indicated. Nadir counts were performed 2 weeks after the start of chemotherapy, or more frequently if necessary. Pulmonary and renal function were monitored closely in all patients. Chest radiographs were obtained as indicated.

Patients were considered to be clinically assessable for response if, before chemotherapy began, they had a tumor mass detectable by physical examination or radiographic studies. A complete response was defined as disappearance of all palpable or radiographic evidence of disease for at least 1 month. Some patients, at the discretion of their attending physician, underwent second-look surgery after completing chemotherapy.

After chemotherapy, patients were evaluated at regular intervals during the first year (monthly during the early part of the study period and every 3 months during the latter part) and at gradually increasing intervals thereafter. Some patients were monitored at M.D. Anderson, and others returned to their referring physician for follow-up. Follow-up information was obtained on all patients.

Information was abstracted from the medical record for all patients. In addition, all patients gave written informed consent and were sent an institutional review board–approved questionnaire. In the questionnaire, we requested information about each patient's tumor status, last physician visit, menstrual history (before, during, and after chemotherapy), use of hormones, and reproductive history (before and after treatment). Those who failed to answer and return their questionnaires were contacted by telephone.

RESULTS

Twenty-six patients with ovarian dysgerminoma were identified as having been evaluated at M.D. Anderson Cancer Center and treated with BEP chemotherapy since 1984. Median follow-up time was 89 months (range, 18 to 183 months). Patient characteristics are listed in Table 1. Fourteen patients (54%) had either stage IIIC or IV disease. Sites of documented metastases included retroperitoneal lymph nodes in 13 patients, omentum in two, uterus in two, fallopian tube in two, supraclavicular lymph node in one, and mediastinum plus pleura in one. Of the seven patients who did not have comprehensive surgical staging, two had cytologically positive ascites (at least stage IC), and one had involvement of the uterine serosa (at least stage IIB). The median number of cycles of BEP chemotherapy was four (range, three to six cycles). One patient received an additional cycle of vinblastine, bleomycin, and cisplatin.

Table 1. Patient Characteristics

Characteristic	No. of Patients (N = 28)	%
Age, years		
Median	19.5	
Range	7-32	
Surgery		
USO	16	62
BSO ± TAH	10	38
Prior treatment		
Surgery	26	96
Radiotherapy	1	4
Treatment setting		
Primary disease stage		
IB	2	8
IC	1	4
IIC	1	4
IIIC	12	46
IV	2	8
Unstaged	7	27
Recurrent disease	1	4
Measurable disease		
Yes	14	54
No	12	46

Abbreviations: BSO, bilateral salpingo-oophorectomy; TAH, total abdominal hysterectomy; USO, unilateral salpingo-oophorectomy.

The one patient who was treated for recurrence had undergone unilateral salpingo-oophorectomy without surgical staging. Twenty months later, she presented with severe back pain and was found to have a massive retroperitoneal recurrence. She received four cycles of BEP chemotherapy and had negative findings at second-look surgery. One of the patients classified as unstaged actually had a second primary dysgerminoma in her remaining ovary before she received BEP chemotherapy. In 1979, she had underwent a unilateral salpingo-oophorectomy for an ovarian dysgerminoma. One year later, she experienced disease recurrence in the paraaortic lymph nodes and received irradiation to the left pelvic and paraaortic lymph nodes as well as to the mediastinum and left supraclavicular lymph nodes. Her second primary ovarian dysgerminoma occurred 7 years later; she received four cycles of BEP and remains disease-free.

Twenty-five (96%) of the 26 patients have remained continuously disease-free. One patient apparently developed a second primary dysgerminoma in her remaining ovary after BEP chemotherapy. She originally underwent right salpingo-oophorectomy without comprehensive surgical staging at an outside hospital. In addition, she had cytologically positive ascites. After referral, she received three cycles of BEP chemotherapy and remained disease-free for approxi-

mately 1 year, at which time she presented with a pelvic mass. Although surgery was recommended, she was lost to follow-up. Nine months later she presented with carcinomatosis and a pleural effusion on imaging studies. She received four cycles of cyclophosphamide and carboplatin. She then underwent hysterectomy, left salpingo-oophorectomy, and surgical staging, with the finding of persistent dysgerminoma in the left ovary. All other biopsy specimens were negative for tumor. She subsequently completed abdominopelvic radiotherapy and remains disease-free.

All but one patient was contacted and either completed the questionnaire or was interviewed by telephone. The one patient who was lost to follow-up was last examined in 1993, at which time she was pregnant. Of the remaining 15 patients who underwent conservative surgery, one was still premenarchal at the time she completed the questionnaire. Ten patients maintained their normal menstrual function during and after chemotherapy; they all had regular menses at the time of this analysis. Five of them were taking oral contraceptives at the time they completed the questionnaire. Three patients had irregular or absent menses during chemotherapy but regained normal menstrual function within 6 months of completing chemotherapy. The one patient who was judged to have developed a new primary ovarian dysgerminoma after BEP therapy failed to resume menses after chemotherapy and subsequently underwent hysterectomy and left salpingo-oophorectomy, as previously detailed. Therefore, 13 (93%) of the 14 patients had returned to their prechemotherapy menstrual pattern at the time they completed the questionnaire.

Five pregnancies have occurred in this group of patients after BEP chemotherapy. One patient had two full-term pregnancies, and a second patient had one full-term pregnancy and is pregnant with her second child. Neither patient had difficulty conceiving, and there is no evidence of birth defects or other disabilities in any of the offspring. Another patient was pregnant at the time of her last visit but has been lost to follow-up.

Two patients had difficulty conceiving. One has an infertile partner, and one patient has had unprotected intercourse for 5 years but has only been attempting to conceive actively for 6 months. She and her partner have not had any infertility evaluation. The remaining 10 patients have not attempted to conceive since completing BEP chemotherapy, most commonly because of a lack of a partner.

DISCUSSION

Ovarian dysgerminoma is the most common type of malignant ovarian germ cell tumor and principally affects girls and young women. For several decades, surgery followed by radiotherapy was the standard treatment for patients with metastatic dysgerminoma.[1,2] Although dysgerminoma is exquisitely radiosensitive and survival rates of 75% to 90% have been achieved with such an approach, fertility is usually sacrificed related to ovarian failure. An occasional patient will resume menstruation after radiotherapy.

A survey of 43 patients treated at our institution with radiotherapy for ovarian dysgerminoma showed that a variety of radiation fields and doses were used.[17] A combination of several fields was often delivered, depending on the sites of disease. These included moving-strip fields (19 to 26 Gy), whole-abdomen fields (20 to 40 Gy), whole-pelvic fields (20 to 30 Gy), pelvic boost (5 to 20 Gy), paraaortic fields (5 to 15 Gy), and mediastinal and left supraclavicular fields (20 to 26 Gy). Three (12%) of 26 patients with an intact uterus spontaneously resumed menses after cessation of hormone replacement therapy, but none became pregnant. These three patients received the following doses: 1) 30 Gy to whole-abdomen, 10 Gy to paraaortic, and 25 Gy to mediastinal and left supraclavicular fields; 2) 20 Gy to moving-strip abdominal, 10 Gy to pelvic boost, and 24 Gy to mediastinal and left supraclavicular fields; and 3) 19 Gy to whole-abdominal, 5 Gy to pelvic boost, and 5 Gy to paraaortic fields. Of note, these three patients were aged 9, 13, and 15 years at the time of their primary treatment.

Postoperative treatment of ovarian dysgerminoma with radiotherapy does not invariably result in ovarian failure. Investigators at the Radiumhemmet reported 14 patients with stage IA dysgerminoma who were treated with unilateral oophorectomy and hemipelvic external irradiation and subsequently delivered 22 children.[18]

In 1984, we began to treat all patients with metastatic dysgerminoma with the BEP regimen, the intent being to achieve efficacy equal to that of radiotherapy while preserving fertility. We initially reported sustained remissions in two patients[12] and subsequently found that all 14 of our patients with dysgerminoma (nine with advanced or recurrent disease) were disease-free after treatment with BEP.[13] The present report expands this experience almost twofold, provides data with longer follow-up time, and details the late effects of platinum-based chemotherapy on reproductive function.

In a previous report of the Gynecologic Oncology Group (GOG) experience, 20 patients with incompletely resected dysgerminoma were treated with either the combination of vinblastine, bleomycin, and cisplatin, or BEP followed by the combination of vincristine, dactinomycin, and cyclophosphamide.[14] Nineteen of 20 patients were disease-free; the median follow-up time was 26 months. Culine et al[15]

subsequently reported on 12 patients who received various platinum-based regimens for newly diagnosed (n = 6) or recurrent (n = 6) dysgerminoma; all patients were disease-free 18 to 180 months after initiation of chemotherapy.

The optimal chemotherapeutic regimen for the treatment of metastatic ovarian dysgerminoma remains unknown. The extreme rarity of this tumor precludes any prospective randomized trial. The dose and schedule of our BEP regimen differ somewhat from those reported by the GOG and by testicular cancer investigators.[14,19] Historically, we have administered cisplatin at a dose of 100 mg/m^2 on day 1 instead of 20 mg/m^2 daily for 5 days in an effort to limit the duration of potentially severe nausea and vomiting. Although we have had a favorable experience with this approach, our method is no longer particularly recommendable because of the availability of better antiemetic medications.

In addition, we have administered etoposide 100 mg/m^2 daily for 3 days instead of 5 days, as used by the GOG and in the treatment of testicular cancer. We did so in an effort to reduce the incidence of neutropenic fever without sacrificing efficacy. Although we are pleased with our results, it may be that our inclination to administer more than the three cycles of therapy recommended by the GOG compensates for our lower total dose of etoposide. Moreover, metastatic dysgerminoma seems to be more chemosensitive than other types of malignant ovarian germ cell tumors. For patients with incompletely resected nondysgerminomatous tumors who receive BEP, 5 days of etoposide is definitely recommended. The eventual elimination of etoposide from the standard regimen may be a worthwhile goal in view of the small but present risk of monomyelocytic leukemia.

We have administered the BEP regimen every 4 weeks rather than every 3 weeks because some of our initial patients' blood counts did not recover until after 21 days. However, this policy has been arbitrary; we are currently administering BEP every 3 weeks if blood counts allow.

In an effort to reduce pulmonary toxicity associated with the BEP regimen, investigators have evaluated the role of bleomycin in patients with good-prognosis testicular cancer.[20-22] The European Organization for Research and Treatment of Cancer randomized good-risk patients to receive four cycles of etoposide and cisplatin with or without bleomycin.[20] In this trial, the etoposide dosage per cycle was 30% less than that used in American trials (360 mg/m^2 *v* 500 mg/m^2, respectively). A higher proportion of patients in the three-drug arm had a complete response (95% *v* 87%). In an Australian randomized trial in which patients received cisplatin and vinblastine with or without bleomycin, the deletion of bleomycin compromised therapeutic efficacy and led to a higher rate of death from cancer (15% *v* 5%).[21] In a similar randomized study conducted by the Eastern Cooperative Oncology Group, good-risk patients received three cycles of etoposide and cisplatin with or without bleomycin.[22] The study was closed early because an interim analysis demonstrated significantly more unfavorable events in the two-drug arm. Thus, the weight of evidence supports retention of bleomycin in the standard chemotherapy regimen for good-risk testicular cancer patients. It is reasonable to extrapolate these findings to patients with ovarian germ cell tumors. However, because dysgerminoma is probably more chemosensitive than other ovarian germ cell tumors, the elimination of bleomycin for this subset remains a worthwhile goal. The GOG has recently completed a trial of the combination of etoposide and carboplatin in patients with completely resected dysgerminoma; however, the results of this trial are not yet mature.

The optimal number of cycles of platinum-based chemotherapy for patients with ovarian dysgerminoma also remains uncertain. Dysgerminoma does seem to be exquisitely chemosensitive, even more so than other malignant germ cell tumors. Our current policy is to administer three cycles for patients with completely resected metastatic disease and four cycles for those with incompletely resected disease. However, there is no scientific basis for this practice.

Of the 26 patients in the present series, four were treated for unstaged tumors apparently confined to the ovary, and two were treated for stage IB disease. All other patients had stage IC disease (n = 1), unstaged disease with at least stage IC or IIA disease (n = 3), or extensive metastatic tumor (n = 16). Our current management strategy includes postoperative chemotherapy for patients with stages IC-IV dysgerminoma and for those with unstaged disease that is at least stage IC as determined from available information. For patients with unstaged disease confined to the ovary (possible stage IA disease), either restaging surgery or observation is probably the best approach. Patients who are restaged and are found to have stage IA or IB disease may be observed, thus avoiding unnecessary chemotherapy. For patients who choose observation but then develop a recurrent dysgerminoma, the curability of the recurrence seems to be high.

Approximately 15% of ovarian dysgerminomas are bilateral, a small proportion of which are occult. Two patients in our series probably had occult contralateral ovarian involvement—the one diagnosed with a new primary ovarian dysgerminoma after being treated with surgery and radiotherapy, and the other diagnosed after BEP treatment. Both patients remain disease-free after further treatment. Such cases raise the question of whether the ovary is a sanctuary

for dysgerminoma. However, it does seem that dysgerminoma arising in a residual ovary is readily curable with further treatment.

The issue of biopsy, bivalving, or wedge resection of a normal contralateral ovary remains somewhat controversial. We continue to recommend that a normal contralateral ovary be left undisturbed because unnecessary biopsy or wedge resection may theoretically lead to future infertility related to peritoneal adhesions or ovarian failure. However, others advocate routine biopsy of a normal contralateral ovary in a patient with ovarian dysgerminoma because detection and resection of a small focus of tumor may allow preservation of a portion of normal ovary. Although the subsequent growth of occult dysgerminoma in the remaining ovary is readily curable with further treatment, the treatment includes resection of the ovary and sacrifice of future fertility. There have been several reports of recurrence of dysgerminoma in the remaining contralateral ovary after conservative treatment.[18,23-26] Gordon et al[24] observed that nine of 27 patients who were treated conservatively subsequently developed tumor in the remaining ovary; none had had biopsy of the ovary performed at the time of the original procedure. Kurman and Norris[27] have estimated that ''at least 6% of dysgerminomas grossly confined to one ovary are associated with occult involvement of the contralateral ovary.'' If a normal contralateral ovary is subjected to bivalving or wedge resection and a small focus of dysgerminoma is grossly identified within the interior of the ovary, then resection of the tumor with preservation of the remaining ovary would be potentially advantageous. On the other hand, identification and resection of microscopic dysgerminoma through a random biopsy or wedge resection might well be problematic, even with frozen-section examination.

When obvious bilateral ovarian dysgerminoma is diagnosed, as it was in two patients in our series, standard therapy consists of bilateral salpingo-oophorectomy. If any normal ovarian tissue can be identified, alternative approaches include unilateral salpingo-oophorectomy plus ovarian cystectomy or bilateral ovarian cystectomy. However, one caveat is that patients with dysgenetic gonads with an XY karyotype should undergo bilateral salpingo-oophorectomy. Three patients in our series had associated gonadoblastoma in the ovary. Two had genetic testing, and both had an XY karyotype; the third patient was not tested.

In a prior report of 40 patients who received chemotherapy for malignant ovarian germ cell tumors after conservative surgery, 67% had regular menses during chemotherapy, 68% had regular menses after chemotherapy, and 83% had regular menses at the time they completed the questionnaire.[28] Only seven of the 40 patients received platinum-based chemotherapy; most received the regimen of vincristine, dactinomycin, and cyclophosphamide. The findings of the present study are very similar. Excluding the premenarchal patient and the patient lost to follow-up, 10 (71%) of 14 patients maintained regular menses throughout chemotherapy and thereafter. All patients but one had regular menses at the time they completed the questionnaire; the one who remained amenorrheic was subsequently diagnosed with dysgerminoma in her remaining ovary, which may account for the lack of ovarian function.

In summary, most patients with metastatic dysgerminoma can expect cure with maintenance of normal reproductive function. Challenges for the future include the search for less toxic chemotherapy and a higher rate of comprehensive surgical staging through physician education or better triage to gynecologic oncologists.

REFERENCES

1. Krepart G, Smith J, Rutledge F, et al: The treatment for dysgerminoma of the ovary. Cancer 41:986-990, 1978

2. Thomas G, Dembo A, Hacker N, et al: Current therapy for dysgerminoma of the ovary. Obstet Gynecol 70:268-275, 1987

3. Einhorn L, Williams S: Chemotherapy of disseminated seminoma. Cancer Clin Trials 3:307-313, 1980

4. Simon S, Srougi M, Goes G: Treatment of advanced seminoma with vinblastine (VBL), actinomycin-D (AcD), cyclophosphamide (CTX), cisplatin (CDDP). Proc Am Soc Clin Oncol 2:132, 1983 (abstr C-517)

5. Samuels M, Logothetis C: Follow-up study of sequential weekly pulse-dose cis-platinum for far advanced seminoma. Proc Am Soc Clin Oncol 2:137, 1983 (abstr C-535)

6. Stanton G, Bosl G, Whitmore W: VAB-6 as initial treatment of patients with advanced seminoma. J Clin Oncol 3:336-339, 1985

7. Cohen S, Goldsmith M: Prolonged chemotherapeutic remission of metastatic ovarian dysgerminoma: Report of a case. Gynecol Oncol 5:299-304, 1977

8. Weinblatt M, Ortega J: Treatment of children with dysgerminoma of the ovary. Cancer 49:2608-2611, 1982

9. Newlands E, Begent R, Rustin G, et al: Potential for cure in metastatic ovarian teratomas and dysgerminoma. Br J Obstet Gynecol 89:555-560, 1982

10. Jacobs A, Harris M, Deppe G, et al: Treatment of recurrent and persistent germ cell tumors with cisplatin, vinblastine, and bleomycin. Obstet Gynecol 59:129-132, 1982

11. Vriesendorp R, Aalders J, Sleijfer D, et al: Treatment of malignant germ cell tumors of the ovary with cisplatin, vinblastine, and bleomycin. Cancer Treat Rep 68:779-781, 1984

12. Gershenson D, Wharton J, Kline R, et al: Chemotherapeutic complete remission in patients with metastatic ovarian dysgerminoma. Cancer 58:2594-2599, 1986

13. Gershenson D, Morris M, Cangir A, et al: Treatment of malignant germ cell tumors of the ovary with bleomycin, etoposide, and cisplatin. J Clin Oncol 8:715-720, 1990

14. Williams S, Blessing J, Hatch K, et al: Chemotherapy of advanced dysgerminoma trials of the Gynecologic Oncology Group. J Clin Oncol 9:1950-1955, 1991

15. Culine S, Lhomme C, Kattan J, et al: Cisplatin-based chemotherapy in dysgerminoma of the ovary: Thirteen-year experience at the Institut Gustave Roussy. Gynecol Oncol 58:344-348, 1995

16. Serov SF, Scully RE, Sorbin LJ: Histological typing of ovarian tumors, in World Health Organization International histological classification of tumors. Geneva, Switzerland, World Health Organization, 1973, pp 17-18

17. Mitchell M, Gershenson D, Soeters R, et al: The long-term effects of radiation therapy on patients with ovarian dysgerminoma. Cancer 67:1084-1090, 1991

18. Björkholm E, Lundell M, Gyftodimos A, et al: Dysgerminoma: The Radiumhemmet series 1927-1984. Cancer 65:38-44, 1990

19. Williams SD, Birch R, Einhorn LH, et al: Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. N Engl J Med 316:1435-1440, 1987

20. DeWit R, Stoter G, Kaye SB, et al: The importance of bleomycin in combination chemotherapy for good prognosis testicular nonseminoma: A randomized study of the ORTC Genitourinary Tract Cancer Cooperative Group. J Clin Oncol 15:1837-1843, 1997

21. Levi JA, Raghavan D, Harvey V, et al: The importance of bleomycin in combination chemotherapy for good-prognosis germ cell carcinoma. J Clin Oncol 11:1300-1305, 1993

22. Loehrer PJ, Johnson D, Elson P, et al: Importance of bleomycin in favorable-prognosis disseminated germ cell tumors: An Eastern Cooperative Oncology Group trial. J Clin Oncol 13:470-476, 1995

23. Asadourian LA, Taylor HB: Dysgerminoma: An analysis of 105 cases. Obstet Gynecol 33:370-379, 1969

24. Gordon A, Lipton D, Woodruff JD: Dysgerminoma: A review of 158 cases from the Emil Novak Ovarian Tumor Registry. Obstet Gynecol 58:497-504, 1981

25. De Palo G, Pilotti S, Kenda R, et al: Natural history of dysgerminoma. Am J Obstet Gynecol 143:799-807, 1982

26. Malkasian GD, Symmonds RE: Treatment of the unilateral encapsulated ovarian dysgerminoma. Am J Obstet Gynecol 90:379-382, 1964

27. Kurman RJ, Norris HJ: Malignant germ cell tumors of the ovary. Hum Pathol 8:551-564, 1977

28. Gershenson D: Menstrual and reproductive function after treatment with combination chemotherapy for malignant ovarian germ cell tumors. J Clin Oncol 6:270-275, 1988