OVARIAN GERM CELL TUMOURS

Effective Date: April 2013

The recommendations contained in this guideline are a consensus of the Alberta Provincial Gynecologic Oncology Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

KEY POINT

A unilateral salpingo-oophorectomy with preservation of the contralateral ovary and uterus for fertility purposes with a full staging procedure is the recommended procedure for germ cell tumors in women of child-bearing age wishing to preserve fertility, even in the presence of metastatic disease.

BACKGROUND

Ovarian germ cell tumours (GCTs) account for approximately five percent of all ovarian cancers and are most commonly diagnosed in young women. In fact, eighty percent of preadolescent malignant ovarian tumors are GCTs. However, these tumours are rare, occurring annually in approximately 3.7 per one million women. [1,2]

There are several types of GCTs, including dysgerminomas, endodermal (yolk sac) tumours, embryonal carcinomas, polyembryomas, choriocarcinomas, teratomas (e.g. immature, mature, monodermal, and highly specialized), and mixed GCTs. [3,4] Diagnosis of ovarian germ cell tumours is based on the gross description of oophorectomy specimens, including the size of the tumour, unilateral or bilateral involvement, surface appearance, and cut surface appearance (solid, cystic, necrotic, hemorrhagic), as well as a microscopic description of the histologic type, histologic grade of tumour, the presence or absence of lymphatic and/or venous invasion, the presence or absence of serosal involvement, the presence or absence of omental involvement, and cytology of peritoneal fluid. [5] Staging is based on the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) [6] and the American Joint Committee on Cancer (AJCC). [7] A detailed description of staging can be found in the Appendix.

GUIDELINE QUESTIONS

1. Are four cycles of etoposide and cisplatin (EP) as effective as standard therapy with three cycles of bleomycin, etoposide, and cisplatin (BEP) with fewer and/or less severe side effects, such as myelosuppression?

2. What support care should be offered to patients with myelosuppression due to chemotherapy and for how long?

3. How should patients be followed up? What tests and frequency of testing are appropriate and for how long?

DEVELOPMENT PANEL

This guideline was reviewed and endorsed by the Alberta Provincial Gynecologic Oncology Tumour Team. Members of the Alberta Provincial Gynecologic Oncology Tumour Team include gynecologic oncologists, radiation oncologists, medical oncologists, pathologists, nurses, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Gynecologic Oncology Tumour Team and a Knowledge Management Specialist from the Guideline

Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

SEARCH STRATEGY

Entries to Medline, EMBASE, and Cochrane (1965 to March 6, 2009) and clinical practice guideline databases were searched for evidence relevant to this topic. Search terms included: ovary* OR ovarian* AND germ cell OR dysgerminoma OR teratoma OR neoplasm AND (1) neutropenia OR myelosuppression AND granulocyte colony stimulating factor OR antibiotics; or (2) chemotherapy OR bleomycin OR etoposide OR cisplatin, with a limit of English language.

The guideline was updated in 2012 and again in 2013 using the following search: PubMed was searched using the terms “ovarian germ cell tumour” or “ovarian dysgerminoma” or “ovarian teratoma.” Results were limited to clinical trials, published through March 2013. Citations were hand-searched for relevant studies, resulting in a total of five retrospective studies in 2012 and two randomized controlled trials and two retrospective studies in 2013. Following a review of the evidence by the Alberta Gynecologic Oncology Team, no major changes were made to the recommendations and the guideline was reaffirmed.

RECOMMENDATIONS

The recommendations outlined in this guideline apply to all women with ovarian germ cell tumours.

The were developed after a review of recommendations from the following sources: the National Cancer Institute, [8] the National Comprehensive Cancer Network, [9,10] and Cancer Care Ontario. [11,12]

Management Options

Recommendations for family physicians or general gynecologists with a young prepubertal and reproductive age female presenting with a complex pelvic mass on examination include:

- imaging (US abdomen and pelvis, and/or CT chest/abdomen/pelvis)
- tumor markers (AFP, HCG, LDH, CA-125) in patients less than 40 years of age
- referral to gynecologic oncologist

When germ cell tumors are suspected based on preoperative work up, in addition to unilateral salpingo-oophorectomy, surgical staging is performed and should include:

- Washings
- Unilateral pelvic and para aortic lymph node sampling
- Peritoneal biopsies and omentectomy

Stage I Tumours

Dysgerminomas

- A unilateral salpingo-oophorectomy with preservation of the contralateral ovary and uterus for fertility purposes with a full staging procedure. If patient has completed child bearing, TAH BSO is acceptable
- Stage IA tumors: observation without adjuvant treatment

- Stage IB/C or incompletely staged: adjuvant chemotherapy

Immature Teratomas

- A unilateral salpingo-oophorectomy with preservation of the contralateral ovary and uterus for fertility purposes with a full staging procedure. If patient has completed child bearing, TAH BSO acceptable
- Stage IA G1: observation without adjuvant treatment
- Stage IA/G2: adjuvant treatment may be considered
- Stage IA G3: post-operative chemotherapy

Other Germ Cell Tumours

- A unilateral salpingo-oophorectomy with preservation of the contralateral ovary and uterus for fertility purposes with a full staging procedure. If patient has completed child bearing, TAH BSO acceptable
- Post-operative chemotherapy

Stage II Tumours

Dysgerminomas

- A unilateral salpingo-oophorectomy with preservation of the contralateral ovary and uterus for fertility purposes with a full staging procedure. If patient has completed child bearing, TAH BSO acceptable
- Adjuvant chemotherapy should be given

Other Germ Cell Tumours

- A unilateral salpingo-oophorectomy with preservation of the contralateral ovary and uterus for fertility purposes with a full staging procedure. If patient has completed child bearing, TAH BSO acceptable
- Adjuvant chemotherapy should be given

Stage III Tumours

Dysgerminomas and other germ cell tumours

- A unilateral salpingo-oophorectomy with preservation of the contralateral ovary and uterus for fertility purposes with a full staging procedure. If patient has completed child bearing, TAH BSO acceptable
- Following maximal surgical debulking, adjuvant chemotherapy is indicated
- Neoadjuvant chemotherapy can be considered for patients with extensive intra-abdominal disease, when initial debulking surgery is not an option

Stage IV Tumours

Dysgerminomas and other Germ Cell Tumours

- A unilateral salpingo-oophorectomy with preservation of the contralateral ovary and uterus for fertility purposes with a full staging procedure. If patient has completed child bearing, TAH BSO acceptable

- Following maximal surgical debulking, adjuvant chemotherapy is indicated
- Neoadjuvant chemotherapy can be considered for patients with extensive intra-abdominal disease, when initial debulking surgery is not an option

Recurrent Tumours

Dysgerminomas
- Chemotherapy
- Radiation therapy in selected circumstances

Other Germ Cell Tumours
- Chemotherapy

Chemotherapy Regimen

For the following tumours: dysgerminomas (Stage II-IV), embryonal tumours, endodermal sinus tumours, and immature Teratomas (Stage I, Grade 2/3, or Stage II-IV)

- A combination of cisplatin and etoposide (EP) or bleomycin, etoposide, and cisplatin (BEP) is preferred because of a lower relapse rate and shorter treatment time.

- 3 day regimen
  - Cisplatin: 35 mg/m^2 in 250 cc NS day 1,2,3
  - Etoposide: 165mg/m^2 in 1000cc NS day 1,2,3
  - Bleomycin: 30 U in 100 cc NS day 1,8,15

- 5 day regimen:
  - BEP: bleomycin (30 units/week); etoposide (100 mg/m^2/day for days 1-5); cisplatin (20 mg/m^2/day for days 1-5)
  - EP: etoposide (100 mg/m^2/day for days 1-5); cisplatin (20 mg/m^2/day for days 1-5)
  - The number of cycles is dependent on the prognosis (Table 1):
    - For “good prognosis” BEP for 3 cycles or EP for 4 cycles is recommended
    - For “intermediate/poor prognosis” BEP for 4 cycles is recommended

- Patients who do not respond to BEP may benefit from the following as salvage therapy (TIP):
  - Cisplatin 35 mg/m^2 day 1, 2, 3
  - Ifosfamide 2 gm/m^2 day 2, 3, 4
  - Taxol 135mg/m^2 day 1

- Chemotherapy is effective and allows for reproductive preservation in patients with an intact ovary, tube, and uterus; radiation therapy is used for patients in whom chemotherapy is not considered appropriate (i.e. CNS disease)

Table 1: Indications used to determine prognosis for dysgerminomas and non-dysgerminomas (Source: *Cancer Treatment Review* 35, 2009; p 563-569)

Prognosis	***Dysgerminoma***	***Non-dysgerminoma***
Good	No non-pulmonary visceral metastases Any LDH, HcG Normal AFP	No non-pulmonary visceral metastases LDH <1.5 times normal; HcG <5000 AFP <1000
Intermediate	Pulmonary visceral metastases present Any LDH, HcG Normal AFP	No non-pulmonary visceral metastases LDH 1.5–10 times normal; HcG 5000–50000 AFP 1000 – 10000
Poor		Non-pulmonary visceral metastases present LDH >10 times normal; HcG >50000 AFP >10000

Supportive Care for Myelosuppression

The decision to provide supportive care should be based on the patient's risk assessment for chemotherapy-induced toxicities, such as febrile neutropenia, neurotoxicity, ototoxicity, and nephrotoxicity. Treatment options available for select patients include amifostine and granulocyte colony-stimulating factor. Indications for the use of these options are included in the recommendations below.

Prophylactic Antibiotic

- If prophylactic antibiotics are being considered, use ciprofloxacin (500 mg po bid) for 10 days starting on day 8 (days 8-17); if the ANC is 0.5 or greater on day 1. If the ANC is <0.5 on day 1, chemo is started but with ciprofloxacin (500 mg po bid) on days 1-17 [13]
- An alternative option is Septra.

Granulocyte colony-stimulating factor (CSF)

- Indications:
    - To maintain dose intensity when there is evidence of an impact on improved survival or to avoid multiple dose reductions
    - To decrease the severity of fever, antibiotic use, or hospitalization associated with febrile neutropenia
    - To avoid infection-associated complications when there is a clear risk and the patient presents with febrile neutropenia during a chemotherapy cycle; if the patient was already taking prophylactic CSF, the treatment should be continued

- Recommendation: prophylactic CSF should not be routinely administered with standard-dose chemotherapy for solid tumours; however, when the anticipated risk of febrile neutropenia and/or medical consequences from febrile neutropenia is high, prophylactic CSF may be considered.
    - Risk of febrile neutropenia is dependent on: [13]
        - Disease type
        - Chemotherapy regimen (for germ cell tumours, BEP is considered to have a risk >20%)

        - Patient risk factors (i.e. age 65 years and older, history of previous chemotherapy or radiation therapy, pre-existing neutropenia or bone marrow involvement with tumor, pre-existing infection/open wounds, recent surgery, poor performance status, poor renal function, liver dysfunction and elevated bilirubin, and treatment intent, curative vs. palliative)

- Myeloid Growth Factors:
    - Agents
        - Filgrastim: 5 mcg/kg/d until post-nadir ANC recovery to normal or near-normal levels by laboratory standards
        - Pegfilgrastim: 6 mg (one dose) per cycle of treatment; start 24 hours after completion of last dose of chemotherapy
    - Administration: subcutaneous route is preferred
    - Alternative dosing schedules in intermediate and high risk patients is not recommended
    - Safety is similar between filgrastim and pegfilgrastim

Follow-up and Surveillance

Dysgerminomas (Stage I) and Immature Teratomas (Stage I, Grade I): observe

Dysgerminomas (Stage II-IV), Embryonal Tumours, Endodermal Sinus Tumours, and Immature Teratomas (Stage I Grade 2/3 or Stage II-IV):

- If a complete clinical response is achieved, observe markers q 3 months, if markers are initially elevated, observe for 2 years
    - Abdominal/pelvic exam
    - Abdominal/pelvic CT if clinically indicated at discretion of the treating physician
    - CXR at discretion of the treating physician
    - Beta-human chorionic gonadotropin, alpha-fetoprotein, lactate dehydrogenase, as clinically indicated
- If there is a residual tumor on radiographic imaging but markers are normal, consider performing a surgical resection or observe
- After 2 years from completing treatment, visits q 6 months

DISCUSSION

Efficacy of Four Cycles of Etoposide and Cisplatin

Platinum-containing chemotherapy regimens have been the preferred treatment for germ cell tumours over the past decade. BEP is the most common regimen used and is usually administered for three cycles in patients with completely resected disease and for four cycles in patients with macroscopic residual disease; however, there is no concensus as to the optimal duration of therapy. [14] Currently in Alberta, the number of cycles is dependent on the patient's risk assessment, with three cycles of BEP recommended for good prognosis patients and four cycles reserved for intermediate and poor prognosis patients.

Due to the toxicity associated with BEP, some work has been done to determine whether or not bleomycin can be omitted from the regimen without compromising efficacy. With respect to GCTs, all of the

information available is from studies in men with testicular GCTs; no studies on women with ovarian GCTs have been published to date. In 1997, the European Organization for the Research and Treatment of Cancer (EORTC) published a study comparing four cycles of BEP versus four cycles of EP (etoposide at 360 mg/m^2) that showed no differences in relapses, time to progression, or survival; however the BEP arm was shown to result in more pulmonary toxicity. [15] Mezvrishvil and Managadze (2006) [16] also showed in men with clinical high risk stage I non-seminomatous germ cell tumors (NSGCT) that there was no difference in response rate or deaths between patients receiving two cycles of BEP and two cycles of EP; however, the latter resulted in less toxicity (e.g. leukopenia).

Culine, et al. (2007) [17] also demonstrated similar response rates among good-risk, metastatic patients (n=262) with NSGCT and no previous chemotherapy who were treated with BEP for three cycles or EP for four cycles. The regimens consisted of etoposide (100 mg/m^2 on days 1–5) and cisplatin (20 mg/m^2 on days 1–5) with or without bleomycin (30 IU on days 1, 8 and 15). The resulting response rates, relapses, and four-year event-free and overall survival rates for patients receiving BEP and EP were 94.7% and 96.8%, 6 and 14, 91% and 86%, and 96% and 92%, respectively. However, toxicity was also similar: grade 3/4 febrile neutropenia and thrombocytopenia were 7% vs. 5% and 6% vs. 8%, for BEP vs. EP, respectively. The follow-up period for that study was only 53 months; however, high response rates (e.g. 98%) and low relapse rates (e.g. 6%) for EP (cisplatin, 20 mg/m^2 on days 1 to 5, and etoposide, 100mg/m^2 on days 1 to 5, at 3-week intervals) for four cycles have been demonstrated with longer follow-up (e.g. median 7.7 years) as well. [18] A phase II/III randomized controlled trial comparing paclitaxel (175 mg/m^2)-BEP with BEP alone demonstrated a 3-year progression free survival advantage for eligible patients in the paclitaxel-BEP group (82.7% versus 70.1%; p=.03). [19]

For patients with relapsed or refractory germ cell tumours, sequential high-dose chemotherapy has been studied in the phase III setting, but was associated with high toxicity-related mortality. A randomized controlled trial comparing single high-dose chemotherapy (VIP plus 3X high-dose carboplatin [1500mg/m^2] and etoposide [1500mg/m^2]) versus sequential high-dose chemotherapy (3X VIP plus 1X high-dose carboplatin [2200 mg/m^2] and etoposide [1800 mg/m^2]) in patients with refractory or relapsed germ cell tumours showed no difference in progression free survival (47% versus 45%, respectively; p=.454) between the groups and a non-significant difference in overall survival (49% versus 39%, respectively; p=.057) in favor of single high-dose. Toxicity-related mortality (14%) in the sequential group warranted that the trial stop early. [20]

Supportive Care for Myelosuppression

Comparative studies on supportive care for the treatment of myelosuppression associated with chemotherapy, within the context of ovarian germ cell tumours, is limited. Guidance on this topic has been gathered mainly from general guidelines on treatment options and meta-analyses on the individual therapies. A large meta-analyses, by Wittman, et al. (2006) [21] was conducted in pediatric oncology patients (n=804) to assess the impact of prophylactic CSF on the risk of febrile neutropenia and included 16 trials. The analysis showed that CSF reduced the rate of febrile neutropenia by 9% (59% vs. 68% in controls; P = 0.03) in patients with solid tumours. The duration of neutropenia, hospital stay, and antibiotic use were also decreased by 3.5 days (P < 0.0001), 1.7 days (P < 0.01), and 2.0 days (P = 0.02), respectively.

An even larger analysis of 17 trials by Kuderer, et al. (2007) [22] in adult patients (n=3,493) with solid tumours or malignant lymphomas compared primary prophylactic granulocyte CSF with placebo and

showed that the risk of infection-related mortality was reduced by 45% in patients treated with CSF vs. controls (P = .018) and that the risk of early all-cause mortality during the chemotherapy period was reduced by 40% (P = .002); furthermore, the risk of febrile neutropenia was reduced by 46% vs. controls (P = .001) and the average relative dose intensity was significantly higher among patients who received CSF (P = .001). Despite these findings, there are risks associated with use of CSF including, most notably, acute impacts on bone health. [23] Therefore, recommendations on the use of prophylactic CSF remain conservative. Prophylactic CSF should not be routinely administered with standard-dose chemotherapy for solid tumours; however, when the anticipated risk of febrile neutropenia and/or medical consequences from febrile neutropenia is high, prophylactic CSF may be considered.

For the reduction of grade 3/4 neutropenia and other chemotherapy-related toxicities, including neurotoxicity, ototoxicity, and nephrotoxicity, amifostine may be considered. A randomized pilot study by Hartmann, et al. (2001) [24] showed that organ toxicity and hematotoxicity can be reduced by the use of amifostine, in patients (n=40) receiving high-dose chemotherapy. However, comparative studies on the use of amifostine are still lacking, especially within the context of germ cell tumours (both testicular and ovarian). Furthermore, amifostine is associated with side effects, such as nausea and vomiting and hypotension; therefore, the benefits of treating these toxicities should be weighed against the side effects and amifostine should not be included routinely in treatment regimens for the purpose of dose maintenance of chemotherapy [10] or for protection against thrombocytopenia. [25]

Follow-up and Surveillance of Patients with Ovarian Germ Cell Tumours

Approximately 75% of GCT recurrences occur within the first year after initial treatment; the most common site is the peritoneal cavity and more rarely the retroperitoneal lymph nodes. [26] Therefore, the objectives of follow-up should be to determine the patient's immediate response to treatment, to allow for early recognition and prompt management of treatment related complications, to allow for early detection of persistent or recurrent disease, and to monitor the efficacy of existing treatment policies and their complications so that modifications can be made. [27]

Unfortunately, there is only limited information as to the optimal follow-up strategy for GCT. As results from ongoing trials are published, this issue may be further addressed; [28] in the mean time, current recommendations for advanced tumours include, as indicated, abdominal/pelvic exam, GI evaluation, ultrasound or abdominal/pelvic CT, chest x-ray, CA-125, inhibin, beta-human chorionic gonadotropin, alpha-fetoprotein, lactate dehydrogenase, CBC, and chemistry profile with LFTs, at a frequency of every two to four months for two years. [9]

GLOSSARY OF ABBREVIATIONS

Acronym	Description
AFP	alpha-fetoprotein
BEP	bleomycin, etoposide, cisplatin
CA-125	antigen
CBC	complete blood count
CSF	colony stimulating factor
CT	computed tomography
EP	etoposide, cisplatin
ESS	endometrial stromal sarcoma
FIGO	Federation Internationale de Gynecologie et d'Obstetrique
GCT	germ cell tumour
GI	gastrointestinal
HCG	human chorionic gonadotropin
LDH	lactate dehydrogenase
LFT	liver function tests
VAC	vincristine, adriamycin, and cyclophosphamide
VeIP	cisplatin, vinblastine, ifosfamide

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of Alberta Health Services, Cancer Care.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2015. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Gynecologic Oncology Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. Alberta Health Services – Cancer Care recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Gynecologic Oncology Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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APPENDIX

Staging of ovarian GCTs is based on the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) and the American Joint Committee on Cancer (AJCC):

- Stage I: growth limited to the ovaries
  - Stage IA: Tumor is limited to one ovary; capsule is intact, and no tumor is present on the ovarian surface. No malignant cells are present in ascites or peritoneal washings.
  - Stage IB: Tumor is limited to both ovaries; capsules are intact, no tumor is present on the ovarian surface. No malignant cells are present in ascites or peritoneal washings.
  - Stage IC: Tumor is limited to one or both ovaries with any of the following: capsule is ruptured, tumor is present on the ovarian surface, malignant cells are present in ascites or peritoneal washings.

- Stage II: growth involving one or both ovaries with pelvic extension and/or implants
  - Stage IIA: Extension and/or implants are present on the uterus and/or fallopian tubes. No malignant cells are present in ascites or peritoneal washings.
  - Stage IIB: Extension to and/or implants are present on other pelvic tissues. No malignant cells are present in ascites or peritoneal washings.
  - Stage IIC: Pelvic extension and/or implants (stage IIA or stage IIB) with malignant cells are present in ascites or peritoneal washings.

- Stage III: growth involving one or both ovaries with microscopically confirmed peritoneal implants outside the pelvis. Superficial liver metastasis equals stage III. Tumor is limited to the true pelvis but with histologically verified malignant extension to the small bowel or omentum.
  - Stage IIIA: Microscopic peritoneal metastasis is present beyond the pelvis (no macroscopic tumor).
  - Stage IIIB: Macroscopic peritoneal metastasis is present beyond the pelvis and ≤2 cm in greatest dimension.
  - Stage IIIC: Peritoneal metastasis is present beyond the pelvis and is >2 cm in greatest dimension, and/or regional lymph node metastasis is present.

- Stage IV: growth involving one or both ovaries with distant metastasis. If pleural effusion is present, there must be positive cytologic test results to designate a case to stage IV. Parenchymal liver metastasis equals stage IV.