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Review Article

Chemotherapy in ovarian germ cell tumors: A systematic review

Christine G. Simone [a], Merry Jennifer Markham [a,*], Don S. Dizon [b]

[a] University of Florida Department of Medicine, Division of Hematology and Oncology, Gainesville, FL, United States
[b] Massachusetts General Hospital Cancer Center, Department of Medicine, Harvard Medical School, Boston, MA, United States

HIGHLIGHTS

- Malignant ovarian germ cell tumors (OGCT) are rare, making up 1% of ovarian tumors.
- Treatment for malignant OGCT has largely been extrapolated from testicular cancer literature.
- Platinum-based chemotherapy improves survival in women diagnosed with malignant OGCT.

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ABSTRACT

Objective. Ovarian germ cell tumors (OGCTs) are rare tumors that comprise a diverse group of histologic subtypes that can either be benign or malignant. Malignant ovarian germ cell tumors (OGCTs) historically carried a poor prognosis, especially among those diagnosed with advanced disease. With the advent of combination chemotherapy, risk of relapse has markedly decreased. There is limited prospective data on the efficacy of specific chemotherapy regimens in the treatment of malignant OGCTs. This article critically reviews the literature pertinent to the treatment of OGCTs with chemotherapy.

Methods. MEDLINE was searched for English language literature on prospective studies on the treatment of malignant OGCTs, focusing on publications since 1995.

Results. As modern chemotherapy regimens have evolved, risk of relapse has decreased with implementation of platinum based regimens in the adjuvant setting. However, the role of neoadjuvant platinum based regimens and treatment of metastatic or recurrent malignant OGCTs remains poorly understood due to lack of randomized control trials.

Conclusions. Malignant OGCTs represent a rare subset of ovarian neoplasms for which focused, prospective clinical trials are needed to determine the most effective therapies.

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Contents

1. Introduction

Ovarian germ cell tumors derive from primordial germ cells of the ovary and may be considered benign or malignant. Malignant ovarian

* Corresponding author at: University of Florida Department of Medicine, Division of Hematology & Oncology, PO Box 100278, Gainesville, FL 32610-0278, United States.
E-mail address: merry.markham@medicine.ufl.edu (M.J. Markham).

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germ cell tumors (OGCTs) are rare, accounting for only 1% of all ovarian tumors with an average age of onset of age <25 years [1]. These may include dysgerminomas and nondysgerminomas (Table 1) [2]. Most cases of endodermal sinus tumor are confined to one ovary at diagnosis. Embryonal carcinoma & immature teratoma are both typically diagnosed at stage I [3]. Dysgerminomas are more likely to be localized to the ovary at the diagnosis, spread in a more predictable fashion, and are considered more sensitive to radiation therapy. In one review of 271 cases of ovarian dysgerminoma, 70% were stage I at the time of diagnosis and most cases were confined to one ovary [3]. Unfortunately, precise data on the incidence of these rare tumors by stage at presentation is not available in the contemporary literature, likely reflecting the rarity of these tumors. Even with extensive disease, most patients with dysgerminoma can be cured [1]. Before the advent of combination chemotherapy in the mid-1960s, patients with advanced-stage malignant nondysgerminomas had a poor prognosis, with risk of relapse ranging from 25% to nearly 100%, depending on the cell type and stage, without adjuvant treatment [4, 5].

One important characteristic of malignant ovarian germ cell tumors is that they are often associated with serum tumor markers such as human chorionic gonadotropin (hCG), alpha fetoprotein (AFP), and lactate dehydrogenase (LDH). These serum markers can be measured during chemotherapy as a measure of response to treatment and in the survivorship phase, during active surveillance. Embryonal cell carcinoma, mixed germ cell tumors, and some dysgerminomas produce hCG. Most dysgerminomas are associated with a normal AFP, but will usually have an elevated LDH. An elevated AFP may be seen in embryonal cell carcinomas, endodermal sinus tumors, mixed germ cell tumors, and some immature teratomas [3].

Because of the rarity of the tumor, there is limited data on the efficacy of specific chemotherapy regimens used in the treatment of OGCT. In this review, we focus on and discuss the key contemporary prospective trials that have shown benefit of platinum-based chemotherapy in the neoadjuvant, adjuvant, and salvage treatment of malignant OGCTs.

2. Methods

For this article, we reviewed the English language literature for prospective studies that evaluated patients with malignant OGCT treated with chemotherapy, either as neoadjuvant or adjuvant treatment. A MEDLINE (PubMed) search of the English literature was performed, with a focus on literature contemporary clinical data published from January 1, 1995, to July 31, 2015. Keywords searched included "ovarian germ cell tumors," "OGCTs," "dysgerminomas," "nondysgerminomas," "embryonal cell carcinoma," "endodermal sinus tumor," "yolk sac tumor," "immature teratoma," "mixed germ cell tumors," "primary ovarian nongestational choriocarcinomas," and "polyembryoma." Additional publications were identified via review of the references lists of publications retrieved during the MEDLINE search. Given the scarcity of prospective data, peer-reviewed original reports with an appropriate number of cases were considered and included. Twenty-nine additional articles were screened and not included, as they were retrospective in design, included males, or were outside our specified date range. This study was conducted with no external funding.

Table 1
WHO classification for malignant ovarian germ cell tumors

Primitive germ cell tumors	Dysgerminoma
	Yolk sac tumor
	Polyvesicular vitelline tumor
	Glandular variant
	Hepatoid variant
	Embryonal carcinoma
	Polyembryoma
	Non-gestational choriocarcinoma
	Mixed germ cell tumors
Biphasic or triphasic teratoma	Immature teratoma
	Mature teratoma
	Solid
	Cystic
	Dermoid cyst
	Fetiform teratoma (homunculus)

Adapted from the WHO Classification of Tumors [2].

3. Neoadjuvant chemotherapy (NACT)

Due to a paucity of prospective, randomized trials, the role of neoadjuvant chemotherapy in malignant OGCTs is not well defined. Talukdar et al. evaluated the role of neoadjuvant therapy in 23 patients who had advanced, bulky disease with poor performance status [Eastern Cooperative Oncology Group (ECOG) performance status 2 or 3] and were not candidates for up-front fertility sparing surgery [6]. All received 4 cycles of bleomycin, etoposide, and cisplatin (BEP) followed by fertility sparing surgery. Their outcome was compared with 43 other patients who had advanced disease (FIGO stages III–IV) during the same period. Complete response was noted in 16 patients (69.6%) and partial response in 5 patients (21.7%). Surgical cytoreduction was successfully performed in 18 of 23 patients, all of whom underwent fertility sparing surgery. Thirteen of these 18 patients had pathologic complete response (CR) after four cycles of neoadjuvant BEP. Of the 5 patients with residual disease identified at surgery, all achieved a CR after two more cycles of BEP. All evaluable patients in this retrospective series (21 of 23) were alive and disease free with mean disease free survival of 211.08 months (95% CI 178.4–243.7). The estimated disease free survival at 10 years was 87%. On subset analysis, there was no difference in outcome between patients with dysgerminoma and nondysgerminoma. Compared to the control group of 43 women with advanced stage disease treated with initial surgery and adjuvant chemotherapy, the neoadjuvant group had similar results during the same time period.

Lu et al. evaluated the role of neoadjuvant therapy in 127 women specifically with yolk sac tumor registered at Peking Union Medical College Hospital from 1995 to 2010. Eighty cases (63%) were classified as having stage III or IV disease according to the FIGO system [7]. Twenty-one patients received neoadjuvant chemotherapy followed by interval debulking surgery and adjuvant chemotherapy. Thirty-two patients underwent primary debulking surgery followed by adjuvant chemotherapy. All patients received standard combination chemotherapy of PEB (cisplatin/etoposide/bleomycin) or PVB (cisplatin/vinblastine/bleomycin) every 3 weeks for one to three cycles pending clinical response. PEV (cisplatin/etoposide/vincristine) was used after the total bleomycin dosage was reached at 250 mg/m^2. Fifteen patients (71%) received three cycles of neoadjuvant chemotherapy, five patients received two cycles and one patient received one cycle. The mean ovarian tumor size decreased significantly after NACT (20.7 $\pm$ 5.7 vs. 17.0 $\pm$ 3.3 cm, $P = 0.016$). The overall rate of optimal cytoreduction with residual disease ≤2 cm was 89%. There was no statistical significant difference in recurrence rate between the NACT and primary debulking surgery groups (14.3% vs. 12.5%). The median follow up was 46 months (range 6–189 months). There was no significant difference between recurrence rate between NACT and surgery followed by adjuvant chemotherapy.

4. Adjuvant chemotherapy

The standard of care for women with malignant OGCT calls for the use of adjuvant chemotherapy in all patients except for those with stage IA grade 1 immature teratoma and stage IA and IB dysgerminoma. For these patients, cisplatin-based combination chemotherapy remains the standard of care. Table 2 summarizes the key prospective trials for adjuvant treatment of malignant OGCTs.

Culine et al. evaluated the role of adjuvant cisplatin-based chemotherapy in dysgerminomas in a small study of 12 patients who received chemotherapy as primary or salvage treatment. Six patients received adjuvant chemotherapy [8]. FIGO stages included stage IA ($N = 1$), IC ($N = 3$), IIC ($N = 1$) and IIIC ($N = 1$). Multiple regimens were given

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