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The Role of Systemic Chemotherapy in the Management of Granulosa Cell Tumors

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Abstract

Objective—Granulosa cell tumors (GCTs) are rare, and the role of chemotherapy in their management is not clearly defined.

Methods—We performed a retrospective cohort study of GCT patients diagnosed from January 1996 through June 2013 at Memorial Sloan Kettering Cancer Center, comparing those who received adjuvant chemotherapy to those who did not. Differences between groups were assessed using the log-rank test. Statistical significance was set at $p < 0.05$.

Results—Of 118 patients, 10 (8%) received adjuvant chemotherapy (1 [1%] of 103 stage I and 9 [60%] of 15 stage II–IV patients). Thirty-two patients (27%) experienced disease recurrence. Four patients had residual disease after initial surgery, and all received adjuvant chemotherapy; each recurred within 24.3 months (median PFS, 8.2 months). The time to first recurrence was longer in patients who did not receive adjuvant chemotherapy. For patients with recurrent disease, receiving chemotherapy after surgery for first recurrence did not seem to improve time to second recurrence versus surgery alone (HR 0.98; $p = 0.965$). Additionally, 12 patients (10%) had a previous

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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diagnosis of breast cancer—an incidence rate 3.22 times higher than Surveillance, Epidemiology, and End Results (SEER) data predicts ($p<0.001$).

Conclusions—Although the numbers were small, in this analysis chemotherapy was not found to improve the recurrence-free interval of patients with GCTs, a finding that requires prospective validation. Residual disease after surgery was associated with poor prognosis. Finally, there was a significantly higher than expected incidence of antecedent breast cancer in this population, an association that deserves further exploration.

INTRODUCTION

Granulosa cell tumors (GCTs) of the ovary arise from the cells that would typically give rise to specialized gonadal stroma surrounding the oocytes. They are the most common type of malignant sex cord stromal tumor (SCST), comprising 2–5% of all ovarian malignancies [1]. According to the most recent Surveillance, Epidemiology, and End Results (SEER) data, approximately 57% are stage I at the time of diagnosis and therefore can be managed surgically. For these patients, long-term disease-free survival rates are approximately 90% [2]. However, outcomes are less favorable for women with higher-stage disease, with 10-year survival rates of 50–65% for stage II disease and 17–33% for stage III or IV disease [2].

Although postoperative or adjuvant therapy is often considered for patients with higher-stage disease, the rarity of these neoplasms makes it difficult to conduct well-designed randomized studies to define the value of this strategy. In addition, GCTs are prone to late relapse [3]. One large multi-institutional review found that 47% of recurrences occurred more than 5 years after diagnosis [4]. Therefore, long periods of follow-up are required to accurately assess outcomes. Some studies suggest that women with advanced-stage or recurrent disease achieve clinical benefit from postoperative chemotherapy [5–11], but others fail to show that the use of chemotherapy is associated with better progression-free survival (PFS) or overall survival (OS) [12–17].

As a result, practice is highly variable. Some centers recommend postoperative chemotherapy for all women with newly diagnosed stage IC–IV disease, most often with bleomycin, etoposide and cisplatin (BEP) or other platinum-based chemotherapy such as paclitaxel and carboplatin; others recommend therapy only for women with residual disease after surgery. Still others do not recommend initial therapy for any stage of disease, treating only at the time of a recurrence. Similarly, there is no standard approach to the management of advanced unresectable or relapsed disease. Radiation therapy (RT) has been shown to induce clinical responses [18], as has chemotherapy with BEP or with other regimens such as cisplatin, vinblastine and bleomycin (PVB), cisplatin, doxorubicin, and cyclophosphamide (CAP) [19], taxanes with and without platinum agents [20, 21], carboplatin and etoposide [22], or doxorubicin alone [23]. One of the only prospective studies in recurrent GCTs, a phase II study of single-agent bevacizumab, resulted in a partial response (PR) in 6 patients (16.7%) and stable disease in 28 patients (77.8%) [24]. Gynecologic Oncology Group (GOG) 187, a phase II study of paclitaxel for ovarian stromal tumors as first- or second-line therapy, is now complete and in follow-up [25]. Other studies

have shown that hormonal therapies such as tamoxifen, leuprolide, or aromatase inhibitors can also be of use [26, 27].

Given the significant variability in the treatment of adult GCTs, including some regimens that carry a risk of significant associated short- and long-term toxicities, more information regarding the potential benefit of each of these therapies is needed. We therefore undertook a systematic review of the large number of patients treated for this disease at our cancer center with the goal of further defining the role for chemotherapy in this orphan disease.

METHODS

Institutional Review Board/Privacy Board permission was obtained for this study. Patients were identified through a prospectively maintained institutional medical records database. The medical records of all patients diagnosed with adult GCTs of the ovary at Memorial Sloan Kettering Cancer Center (MSKCC) from January 1996 through June 2013 were reviewed, and pertinent information was abstracted. Data collected included demographic information; clinical, surgical, chemotherapy, and radiotherapy information; and dates and nature of follow-up.

The inclusion criteria were as follows: patients must have received a diagnosis of adult GCT, and patients must have been seen at MSKCC for evaluation and treatment of this diagnosis. The diagnosis of GCT was confirmed at MSKCC by an expert gynecologic pathologist and/or reviewed at the gynecologic pathology consensus conference. Patients were excluded if adult GCT was diagnosed incidentally while undergoing surgery for a separate gynecologic malignancy that drove treatment planning decisions. One hundred twenty-five patients were identified. Seven patients were excluded: 6 who had a concurrent gynecologic malignancy, and 1 who upon pathology review was found to have anaplastic ovarian carcinoma rather than a GCT. This left 118 assessable patients who were included in this study.

Statistical Analysis

The endpoints selected for analysis included time to first recurrence (RFS1), time to second recurrence (RFS2), and OS. RFS1 was defined as the time from histologic confirmation of diagnosis to the time of documented recurrence via an imaging study. RFS2 was defined as the time from initial therapy for first recurrence, which could be either surgical or systemic therapy, to the time of documented second recurrence via an imaging study. OS was defined as the time from histologic confirmation of diagnosis to death from any cause.

Landmark analysis was used to evaluate RFS1 for patients who received adjuvant therapy (defined as therapy initiated less than 12 weeks after initial diagnosis) and for those who did not to see if there was a difference between the groups. Among patients receiving adjuvant chemotherapy, the longest time to chemotherapy initiation was 11 weeks postoperatively, so this was set as the landmark time after which patients could be analyzed for this data point. Age, presence or absence of residual disease after initial surgery, and complete surgical staging at time of diagnosis were also evaluated to see whether these variables were associated with a difference in RFS1.

In order to evaluate the treatment difference (for example, surgery alone versus surgery followed by adjuvant systemic therapy) for RFS2, the covariate was considered as a time-dependent covariate.

Descriptive statistics were calculated for all patients and for specific subgroups. The differences between groups with respect to OS and time to recurrence were assessed using the log-rank test. Statistical significance was set at a $p < 0.05$. Multivariate analysis was unable to be performed given the small number of events.

RESULTS

Patient and Disease Demographics

There were 118 patients with adult GCT included in our analysis. See Table 1 for patient and disease demographics. The median age at diagnosis was 49 (range, 23–87). The majority of patients (87%) had stage I disease; 69% were initially diagnosed with stage IA or IB disease and 19% with stage IC disease. The remaining 13% had stage II–IV disease at diagnosis.

All of the patients underwent upfront surgery. Fifty-seven patients (48%) underwent a complete surgical staging procedure for ovarian cancer, and 61 (52%) did not. Four patients (3%) had gross residual disease present after upfront surgery, and 114 (97%) had no gross residual disease. The presence of gross residual disease after upfront surgery was a poor prognostic factor, with a median PFS of 8.2 months and all patients recurring within 24 months (Supplemental Table 1).

Ten patients received adjuvant chemotherapy, and 2 patients received adjuvant pelvic RT. All but one of the patients who received adjuvant therapy had stage II–IV disease (Table 1). Of the 10 patients who received chemotherapy, 5 (50%) received combination chemotherapy including a platinum and etoposide, and in three instances, bleomycin; 4 (40%) received combination chemotherapy with a platinum and a taxane; and one patient (10%) received carboplatin and cyclophosphamide. Only one patient with stage I disease received adjuvant therapy (stage IC). Four patients with stage II–IV disease did not receive adjuvant chemotherapy. One had a difficult recovery from surgery and multiple comorbid conditions precluding treatment; the other 3 made the decision, along with their providers, not to undergo systemic treatment.

Adjuvant Chemotherapy and Recurrent Disease

In the entire cohort of 118 patients, there were 32 recurrences (27%), 2 cases of primary refractory disease (progression during adjuvant chemotherapy), and 1 death with no recurrence. The median follow-up for the remaining 109 patients was 36.8 months (interquartile range, 14.2–80.0 months). The median RFS1 was 159 months for stage IA–IB patients, 62.3 months for stage IC patients, and 35.2 months for stage II–IV patients (Supplemental Table 1). These differences were statistically significant with a p -value of < 0.001 (Figure 1).

RFS1 was also analyzed with respect to whether or not patients received adjuvant chemotherapy, defined as chemotherapy initiated within 12 weeks postoperatively. Those who did not receive adjuvant therapy had a significantly longer median PFS and a significantly higher 3-year PFS rate than those who received adjuvant therapy ($p<0.001$). Kaplan-Meier curves are shown in Figure 2.

Management and Outcome Following First Recurrence

Thirty-two patients experienced at least one recurrence. Of these patients, 11 (34%) were treated at first recurrence with surgery only, 15 (47%) with surgery combined with chemotherapy and/or hormonal therapy, 3 (9%) with chemotherapy only, 1 (3%) with hormone therapy only, and 2 (6%) with pelvic RT only. Outcome by treatment modality received is shown in Supplemental Table 2. During follow-up, 23 patients (72%) had a second recurrence, 2 (6%) were refractory to further treatment, 1 (3%) died without a second recurrence, and 6 (19%) were alive at the time of last follow-up with no further recurrence. The median follow-up for the 6 patients who experienced a first recurrence but no second recurrence was 19.3 months (range, 7.8–115.3 months). The median RFS2 was 25.6 months, and the 1-year RFS2 rate was 80.6% (Figure 3).

Because there were such small numbers of patients who received each type of treatment for first recurrence, it was not possible to draw conclusions overall about which method was superior. We performed time-dependent covariate analysis of outcomes in the two largest groups, which consisted of patients who received surgery alone ($n=11$) and patients who received surgery followed by adjuvant systemic therapy ($n=15$). The p -value was not significant ($p=0.965$), and the outcomes appeared to be essentially the same (HR 0.98 [0.38–2.53]).

Overall Survival

OS was excellent in this patient population. There were 8 deaths among the 118 patients, leaving 110 patients alive at a median follow-up time of 57.7 months (interquartile range, 20.8–110.8 months). Median OS was not reached, with 3-year OS rates of 100% in stage IA–IB patients, 100% in stage IC patients, and 90.9% (95% CI, 50.8%–98.7%) in stage II–IV patients. OS was shorter in patients with later-stage disease ($p=0.001$; Figure 4).

SCSTs and Breast Cancer

Twelve (10%) of the 118 GCT patients had had a diagnosis of breast cancer prior to the diagnosis of their SCST, with breast cancers diagnosed at a median age of 49.3 years. Accounting for differences in race by splitting all patients into those who self-identified as white ($n=7$) and those who self-identified as black ($n=5$), we used SEER incidence rates of breast cancer in white and in black women to estimate the expected number of breast cancers that would be seen in each group and to evaluate how the observed number in our study differed (Supplemental Table 3). The observed number of breast cancers in our white patients was 2.57 times higher than what would be expected based on SEER data; in the black population, the observed incidence was 4.95 times higher. The p -values were significant for both racial subcategories ($p=0.021$ for white patients, $p=0.004$ for black patients) and for the two groups combined ($p<0.001$) (Supplemental Table 3). In addition,

we used SEER data to calculate age-incidence rates for SCSTs and found that much like breast cancer [28, 29], the age-specific incidence rises sharply until menopause and then the rate of increase drops sharply (Figure 5).

Since many of these cancers were diagnosed and treated outside of our institution, data on the nature of the breast cancer and therapy were somewhat limited, but 5 (100%) of 5 patients who had available estrogen receptor/progesterone receptor (ER/PR) test results in the MSKCC medical records tested positive for both ER and PR, and 7 patients were noted to have received adjuvant tamoxifen after their breast cancer diagnosis. The median body mass index (BMI) for these patients at the time of SCST diagnosis was 26.7 (range, 21.8–42.3). Three (25%) of 12 patients had a BMI >30 kg/m². Four patients (33%) were nulliparous and 2 (17%) had had only one pregnancy.

DISCUSSION

Determining the optimal therapeutic regimen for ovarian GCTs has been difficult for several reasons. These tumors are rare, making it difficult to conduct definitive studies. In addition, the slowly progressive nature of these tumors requires long-term follow-up to draw meaningful results about PFS and OS. Many prior studies suggest that while there is clinical activity associated with chemotherapy in GCTs, it may not be enough to produce long-term responses. One study of 7 patients treated with BEP for metastatic SCST reported responses in 6 patients (83%), but only 1 patient (14%) had a durable remission [30]. Another study of patients with incompletely resected stage II–IV disease found that while 11 patients (69%) with advanced-stage primary tumors and 21 (51%) with recurrent disease remained progression-free at the end of the study, many of these had stable disease or non-measurable response rather than definitive tumor shrinkage [31]. There are select studies that have shown a PFS advantage in favor of adjuvant chemotherapy. Recently published data from MITO-9 showed a PFS advantage in 8 patients treated with adjuvant chemotherapy compared with 27 patients who did not receive adjuvant chemotherapy (72.5 months vs. 48 months, respectively) [32]. Currently, adjuvant malignant germ cell regimens or paclitaxel and carboplatin are recommended (National Comprehensive Cancer Network [NCCN]-category 2B) [33] for patients with stage II–IV or recurrent GCT of the ovary following complete initial surgical resection.

In our large experience of patients treated for GCTs, we found that even when controlled for stage, adjuvant therapy did not appear to improve RFS1; in fact, patients who received adjuvant therapy appeared to recur sooner. Our study, however, was limited by the small number of patients who received adjuvant chemotherapy, and as such, we were unable to adequately estimate the effect of stage on outcome to adjuvant therapy. Confounding or interaction with stage is an important issue for future, larger studies to evaluate. There were also not enough patients in this study who received hormone therapy or pelvic RT to sufficiently analyze outcomes with regard to those therapies.

There are limitations to the retrospective data from our study and others. It is possible that patients who received chemotherapy had more widespread disease or other features that potentially put them at higher risk for recurrence postoperatively than those who did not.

Alternatively, those who did not receive chemotherapy may have had a poorer performance status than those who did and thus might have been deemed unsafe for treatment. Given the large number of patients in our study initially treated at outside institutions, it was not possible to analyze performance status at diagnosis, which is a limitation of our study. In addition, the combinations of chemotherapy agents and doses of agents given varied widely, making it difficult to conclude the relative value of one regimen over another.

Despite the limitations of our analysis, this study does raise important questions about the value of chemotherapy in this slow-growing disease. Given the present data, it seems possible that even after accounting for these potential unmeasured confounders, a significant clinical benefit may not be observed in patients receiving chemotherapy following surgery compared to surgery alone. Given the potential long-term toxicities of chemotherapy, such as secondary acute leukemia [34,35] and cardiovascular disease [36], and the fact that none of these small studies has shown an OS benefit, the true magnitude of PFS benefit is important to further define. GOG study 264 (ClinicalTrials.gov Identifier NCT01042522) is an ongoing randomized phase II study of BEP versus carboplatin and paclitaxel in newly diagnosed stage II–IV and recurrent sex cord stromal tumors, but the questions raised by this study and others suggest the need for additional prospective research in this population, ideally with a control arm that includes no systemic treatment.

The lack of obvious benefit from chemotherapy also points to the need for treatment options more directly targeted uniquely at this tumor type. Whole-transcriptome exome sequencing of four granulosa cell tumors identified a single, recurrent somatic mutation (402C-->G) in FOXL2 that was present in almost all (86/89) morphologically identified adult-type germ cell tumors as well [37]. This suggests that mutant FOXL2 may be the key driver in the pathogenesis of adult-type granulosa cell tumors, and therapies targeting this mechanism may prove to be more useful and less toxic than traditional chemotherapy.

Interestingly, we also found a possible association between granulosa cell tumors and a diagnosis of breast cancer in this patient population. There is one other recent study that noted similar findings, a retrospective review of 163 Danish patients with granulosa cell tumors of the ovary in which 7 patients were diagnosed with breast carcinoma and 1 with Paget's disease of the nipple [38]. In our study, 12 (10%) of 118 patients were diagnosed with breast cancer prior to their SCST diagnosis, a much higher incidence than would be expected. Given that immunohistochemical staining for ER/PR was positive in 100% of the tumors that were tested, it could be hypothesized that there is a common hyperestrogenic state that drives the development of breast cancer and SCSTs in this population. The steady increase in age-specific incidence rates of both breast cancer and SCSTs until menopause provides further support for this hypothesis. It is also possible that in cases in which tamoxifen was administered for the treatment of hormone-receptor positive breast cancer, metabolites of tamoxifen that act as estrogen agonists could have contributed to the development of subsequent SCSTs [39]. There are three case reports of granulosa cell tumors after tamoxifen reported in the literature [39–41]. The association between breast cancer and GCTs should be further explored.

In this retrospective analysis, adjuvant chemotherapy did not improve the recurrence-free interval of patients with GCTs, suggesting the need for prospective study. OS in this patient population was generally good. Given the significant short- and long-term toxicities associated with the chemotherapy regimens typically considered in this disease, observation following complete surgical resection may be a reasonable option for management. We also discovered a significantly higher than expected incidence of antecedent breast cancers in this population—an association that needs to be further explored.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research Highlights

- We reviewed the records of 154 ovarian sex cord stromal tumor (SCST) patients.
- Adjuvant chemotherapy did not improve outcomes, regardless of disease stage.
- The incidence of breast cancer was higher than expected and is worthy of further study.

Figure 1.
Recurrence-free survival (RFS1) by stage

Figure 2.
Recurrence-free survival (RFS1) stratified by stage, by primary adjuvant therapy choice. A.
Stage I disease. B. Stage II–IV disease

RFS Curve for Recurred Pts

Figure 3.
Time from first to second recurrence (RFS2) for patients who experienced a first recurrence

Figure 4.
Overall survival (OS) by stage

Figure 5.
Age-specific incidence rates for sex cord stromal tumors in US females, 1980–2011

Table 1

Patient and disease demographics

Variables	N	%
Total	118	
Age at diagnosis		
Median (Mean)	49 (50.3)	
Range	23–87	
Stage		
IA–IB	81	68.6%
IC	22	18.6%
II	68	5.1%
III	1	6.8%
IV		0.9%
Complete surgical staging procedure performed		
Yes	57	48.3%
No	61	51.7%
Initial adjuvant therapy (yes/no) by stage		
I	103	
Received adjuvant therapy	1	1.0%
Did not receive adjuvant therapy	102	99.0%
II–IV	15	
Received adjuvant therapy	11	73.3%
Did not receive adjuvant therapy	4	26.7%
Gross residual		
No	114	96.6%
Yes	4	3.4%
Full staging		
No	61	51.7%
Yes	57	8.3%