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Review Article

Advanced Granulosa Cell Tumors of the Ovary: A Review with a Focus on Current and Novel Therapeutic Approaches

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ABSTRACT

Granulosa cell tumor (GCT) is the most common nonepithelial ovarian malignancy. Still, it is considered rare, with a paucity of high-level evidence guiding management, particularly in the metastatic setting. Advancements in molecular pathology allowed the identification of several targetable mutations that play an important role in GCT pathogenesis. Although current management approaches rely on guidelines extrapolated from the more common epithelial subtype, the unique histopathologic and molecular characteristics of GCTs entail a more focused approach. Systemic therapy remains the cornerstone treatment for advanced disease, and although chemotherapy has been the standard for decades, targeted treatments have gained considerable attention lately. Due to the rarity of this disease, validation of new therapies in large trials is the rate-limiting step for developing evidence-based recommendations. This review sheds light on pathogenesis, clinical and molecular characteristics, and prognostic factors, and discusses current treatment options including the role of novel therapies and immune checkpoint inhibitors in advanced GCT.

Keywords: granulosa cell tumors, rare cancers, FOXL2

BACKGROUND

Granulosa cell tumors (GCTs) arise from the sex cords of the ovary. Although considered a rare cancer, with an incidence in the United States of about 1 in 100,000, it is the most common nonepithelial tumor, representing about 2–5% of all ovarian tumors and 70% of all sex cord–stromal tumors (SCSTs).[1,2] Ovarian GCTs can be subclassified into two subtypes: a juvenile subtype that comprises 5–15% of all cases, usually diagnosed in the first 3 decades of life, including extremely rare cases of infants, with a median age at diagnosis of 7–9,[3,4] and an adult subtype that comprises 85–95% of cases, diagnosed at any age, with a median age of 46.[5] The two subtypes have different genomic aberrations and may exhibit different clinical behavior.[6,7] Furthermore, although early-stage GCTs are known for having low risk of recurrence, some of these tumors display aggressive clinical behavior manifested by high potential for recurrence, dissemination, and resistance to therapy. Tumor-specific treatment guidelines are lacking due to scarcity of prospective randomized trials given the relative rarity of this disease.

CLINICAL PRESENTATION

Clinical manifestations of GCTs vary depending on age and menstrual status. Juvenile GCTs often present as an abdominal mass or distension and can exhibit signs of hormonal overproduction. In children, the initial symptoms may include precocious isosexual pseudopuberty characterized by hyperestrogenism with concomitant thelarche, pubarche, vaginal bleeding, and advancement of bone age.

In young adults, the tumor may cause menstrual irregularities that mimic polycystic ovarian syndrome. In very rare cases, the tumor may produce androgens, leading to virilization or contrasexual pseudopuberty.[8–10] Abdominal symptoms of adult GCTs can resemble those of the juvenile subtype. However, because older women are typically affected, dysfunctional uterine bleed may occur as a result of hyperestrogenism, which subsequently can lead to endometrial hyperplasia and uterine cancer.[11] Rarely, the tumor may rupture, resulting in an acute presentation as hemoperitoneum.[12]

GCT is commonly unilateral, but bilateral presentations have been reported, particularly in the setting of congenital syndromes like Goldenhar, Potter, and Maffucci.[13–16] Other hereditary syndromes have also been occasionally associated with GCT, including Peutz-Jeghers syndrome and Ollier disease (enchondromatosis).[17–19] Despite their indolent growth, adult GCTs are associated with a higher risk of relapse compared with the juvenile subtype. After curative-intent surgery for locoregional disease, recurrence occurs in about 20% of cases, typically after a latent period of 5–10 years, and may even occur after a latent period of over 20 years.[5] In a case series of 36 patients with International Federation of Gynecology and Obstetrics (FIGO) stage 1 adult GCT, 12% of patients experienced a relapse after a median follow-up of about 10 years.[11]

The appearance of GCT on imaging is similar to that of its gross anatomy. Adnexal masses can be multilocular or unilocular, with thin- or thick-walled structures, and can appear as homogenous cystic or heterogeneous solid lesions with internal cystic component.[20,21] In one of the largest series examining radiographic appearance, Stine et al[22] demonstrated that the majority of GCTs appear as complex cysts (98%), most commonly containing cystic and solid components. In 70% of patients, the tumor measured over 10 cm on CT scans.

PATHOGENESIS AND MOLECULAR LANDSCAPE

The majority of adult GCT cases harbor a recurrent somatic mutation in the forkhead box L2 (*FOXL2*) gene, which encodes a transcription factor required for normal granulosa cell development.[23,24] The mutation, present in 95–97% of adult GCT cases, is infrequent in the juvenile GCT, where it accounts for 10% or less of cases.[25,26] *FOXL2* is also implicated in activating the transcription of the gene encoding the pituitary gonadotropin-releasing hormone receptor (*GNRH-R*) and repressing the promotor of the steroidogenic acute regulatory protein (*StAR*) gene, which controls a rate-limiting step in steroidogenesis.[27] Moreover, the mutant *FOXL2*, through an acquired novel DNA motif, gains the ability to bind SMAD4, forming a FOXL2/SMAD4/SMAD2/3 complex that enhances transcription of nearby genes involved in epithelial-to-mesenchymal transition.[28] Hence, the role of *FOXL2* mutation in the pathogenesis of adult-type GCT is now widely accepted as a promoter of cell proliferation, survival, and hormonal responsiveness.

Establishing a molecular diagnosis using *FOXL2* mutation status can be crucial in cases with histologic similarities to other tumors such as gonadal stromal tumor and benign luteomas of pregnancy, or unrelated highly malignant tumors like poorly differentiated carcinomas, mixed mesodermal tumor, and sarcomas.[29] In addition to *FOXL2*, a mutation in the promoter region of the telomerase reverse transcriptase (*TERT*-124C>T) was identified in about 40% of adult-type GCTs and is associated with a more aggressive clinical behavior.[30] Several other cytogenetic aberrations and aneuploidies, including trisomy 12, trisomy 14, monosomy 22, monosomy X, and deletion of chromosome 16 or 17, have been reported, with no clear prognostic correlation.[30–33] In a cross-sectional study that aimed to molecularly profile 423 tumor samples of adult GCTs, *FOXL2* was detected in 100%, *TERT* promoter mutation in 56%, *KMT2D* mutation in 16.8%, *CDKN2A/B* deletions in 10.2%, *TP53* mutation in 8.3%, *MTAP* deletion in 5.8%, and *PIK3CA* mutations in 5.4%.[34]

Immunologically, GCT is considered a cold tumor, typically with negative PD-L1 expression and low tumor mutation burden, as described in 67 samples in the case series published by Hillman et al.[34] In another series that examined 29 adult-type GCT samples, PD-L1 was negative and CD8+ tumor-infiltrating lymphocytes were scarce in all tumor samples.[35]

HISTOPATHOLOGY

The two subtypes appear similar in many aspects on gross and microscopic anatomy. Grossly, GCTs have the appearance of solid and cystic masses that can be uni or multilocular, with areas of necrosis or hemorrhage. On microscopic examination, both subtypes are composed of small cells with scant pale cytoplasm and grooved (coffee bean) nuclei in diffuse growth patterns. However, other patterns have been described, including macro- and microfollicular, insular, trabecular, or mixed patterns.[32,36] Less commonly, Call-Exner bodies, which are small cystic spaces of debris surrounded by granulosa cells, can be seen on microscopic examination.[32]

Adult GCTs typically have fewer mitotic figures, whereas the juvenile subtype may show higher mitotic activity. Additionally, the juvenile subtype is characterized by follicular formations of various shapes and sizes. Another histologic pattern that has been observed is the anaplastic variant of the juvenile subtype, which exhibits numerous cystic compartments and syncytiotrophoblast-like giant cells on gross microscopy.[7] On the other hand, adult GCTs with foci of hepatoid cell differentiation and negative staining for inhibin alpha is a rare histologic variant.[37] GCTs have been diagnosed during pregnancy, where the tumor is usually dominated by round luteinized cells with abundant cytoplasm.[36,38] The sarcomatoid GCT variant is an aggressive tumor with a high mitotic rate and high Ki-67 proliferation index, usually indicating a worse prognosis.[39] Testing for FOXL2 p.C134W by nucleic acid sequencing can aid in diagnosing equivocal cases of adult subtype.[25,29]

IHC is a useful tool for diagnosing GCT, which typically stains positively for CD99 and inhibin. Other markers, such as vimentin, calretinin, WT1, and smooth muscle actin, may also show positive staining.[38,40] In addition, the majority of GCTs express estrogen receptor (ER). However, a case series report of ER-subtype staining of 32 primary and recurrent GCTs showed that positive

staining for ER-β was detected in all patients with strong nuclear and weak cytoplasmic localization. In contrast, a low-intensity nuclear-localized ER-α staining was detected in only 30% of cases. Moderate to high nuclear staining for progesterone receptor (PR) and androgen receptor (AR) was detected in all cases.[41]

ENDOCRINE BIOMARKERS

Hormonal overproduction by malignant granulosa cells is the hallmark of nearly all GCTs. These hormones can serve as a valuable tool in diagnosing and monitoring the recurrence and response/progression of early-stage and metastatic patients, respectively. Inhibin A and/or B is produced by the granulosa cells in almost all patients, and its levels correlate with disease activity and tumor burden.[17,42,43] Anti-Müllerian hormone, belonging to the TGF-β family, is also a useful tumor marker, with a reported sensitivity rate of 89% and specificity of 93% in GCTs, alongside inhibin.[44,45] However, inhibin is not specific for the diagnosis of GCT because it can also be produced by other ovarian tumors.[42,43] Although estradiol is also produced by the granulosa cells, its levels may not always be a reliable marker to monitor metastatic disease because there is no consistent correlation of estradiol levels with tumor burden. In addition, up to 30% of GCTs may not produce estrogen.[45,46] Pituitary gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), are usually very low, as would be expected, due to negative feedback mediated primarily by inhibin.

PROGNOSTIC CHARACTERISTICS

Stage at diagnosis remains the most significant prognostic factor for long-term outcomes.[32] Ten-year survival decreases from approximately 90% in stage I to about 17–33% in stages III and IV combined. Tumor rupture seems to portend a strong relapse risk. The juvenile subtype generally has a lower risk of recurrence compared with the adult subtype.[47,48]

Histologic evidence of lymphovascular space invasion and the presence of a mitotic index of four or more mitoses per 10 high-power fields are independent predictors of recurrence, although this is not a consensus.[49–51] In a single-institution cohort of 125 patients of Black or African American race, nuclear pleomorphism, high HER2 expression, high CD56 expression, and high SMAD3, in addition to stage and mitotic activity, were associated with increased risk of recurrence.[51] Furthermore, tumors with a FOXL2 mutation have a higher expression of FOXL2 protein by IHC, which was identified as an independent predictor of worse survival outcomes.[26]

TREATMENT

Primary Tumor

The majority of juvenile GCT subtype cases are diagnosed in stage 1, with unilateral oophorectomy or salpingo-oophorectomy being curative and preserving fertility.[52] In adult GCT, however, extensive surgery is required to include total hysterectomy and a unilateral salpingo-oophorectomy with staging being a reasonable approach.[53]

Recurrent Tumor

Approximately 20% of adult GCTs are estimated to recur after a median time of 5 years from initial diagnosis.[54,55] The current standard of care is resection of the recurrent tumor if surgically feasible.[52]

When considering treatment for inoperable or metastatic disease, systemic therapy with palliative intent remains the cornerstone of treatment. There are several options, including conventional cytotoxic chemotherapy, hormone-based (endocrine) therapy, radiation, and novel or targeted therapy (Table 1). The rarity of this disease and the lack of randomized clinical trials necessitate that most of the evidence is derived from small retrospective studies and case series. Due to the risk of peritoneal dissemination, some experts recommend the use of hyperthermic intraperitoneal chemotherapy, as an adjunct to cytoreductive surgery.[56] Nevertheless, this approach should still be considered experimental pending further evidence.

Chemotherapy

Platinum-based chemotherapy regimens have been used with varying success in metastatic disease. Prior to the widespread adoption of cisplatin, etoposide, bleomycin (BEP), anthracycline-based regimens were routinely used in front-line settings.[57] In a small case series of 10 patients with chemotherapy-naïve advanced or recurrent GCT, residual disease post–debulking surgery was treated with CAP (cyclophosphamide, doxorubicin, cisplatin), resulting in a response rate of 60% (6 patients).[58] Another regimen previously used in advanced GCT is PVB (cisplatin, vinblastine, bleomycin), which, in small series, produced a response rates of 66% (4 of 6).[59] Later on, BEP emerged as an effective regimen with lower neuropathy incidence and lower cardiac toxicity, albeit with higher risk of pulmonary toxicity. In a small retrospective series of nine chemotherapy-naïve patients with advanced GCT, BEP resulted in a response rate of 22% (2 patients), with a median progression-free survival (mPFS) of 12 months and median overall survival (mOS) of 50 months.[60]

A phase II trial looked at BEP activity in patients with advanced or incompletely resected ovarian stromal tumors, the majority of which were granulosa cell. Among 38 evaluable patients, 14 (37%) had negative findings on second-look surgery, the primary outcome measure for this trial.[61]

Table 1. Systemic therapies of interest in GCT

Study	Regimen	Setting	Response Rate	mPFS	mOS	Histology
Chemotherapy						
van Meurs et al[60]	BEP	Chemotherapy-naïve recurrent adult	22% (2/9)	12 mo	50 mo	SCST (majority GCT)
Burton et al[65]	Paclitaxel phase 2	Second line, recurrent, adult	29% (9/31)	10 mo	73.6 mo	SCST
Ray-Coquard et al[81]	Paclitaxel vs paclitaxel + bevacizumab randomized phase 2	Second line, relapsed after at least 1 platinum-based chemotherapy, adult	25% (8/32) (paclitaxel) 44% (12/28) (combination)	14.7 vs 14.9 mo	NR in either group (crossover allowed)	SCST (majority GCT)
Pecorelli et al[95]	PVB	Front line, advanced and recurrent $N = 25$	52% (13/25)	13.9 mo	25.4 mo	SCST (GCT and granulosa-theca cell tumors)
Uygun et al[96]	CAP	Front line postsurgery residual $N = 14$	71% (10/14)	Not reported	Not reported	GCT (16 year-olds included)
Brown et al[62]	BEP vs taxane-based regimens	Front line, recurrent $n = 10$ vs 37 for BEP and taxane, respectively	71% (7/10) vs 37% (14/37)	11.2 vs 7.2 mo	NR	SCST
Pautier et al[64]	BEP	Front line metastatic or recurrent, adult $N = 20$	90% (18/20)	25 mo	46 mo	GCT
Brown et al[80]	Bevacizumab ($n = 36$)	Recurrent, unlimited prior therapy, adult	16.7% (6/36)	9.3 mo	NR	SCST (88.9% GCT)
Brown et al[66]	BEP vs CP ($n = 32$ vs 31) randomized	Front line (newly diagnosed and recurrent chemo naïve, adult) $N = 63$	Not reported	19.7 mo vs 27.7 mo	Not reported	SCST (87% GCT)
Endocrine therapy						
Alhilli et al[70]	Anastrozole or letrozole	$N = 7$, recurrent, adult (case reports)	100%	> 12 mo	NR	GCT
Banerjee et al (PARAGON)[77]	Anastrozole	$N = 41$, recurrent, adult	10.5% (CBR at 3 mo 78.9%)	8.6 mo	NR	GCT
Immunotherapy						
How et al[82]	Pembrolizumab	$N = 5$; 4 adults, 1 juvenile; recurrent	0% (2 pts had SD)	NR	NR	GCT
Novel combinations						
O'Sullivan Coyne et al[85]	Temozolomide + TRC102	$N = 2$ adults, recurrent	100% (2 of 2 pts)	> 12 mo	NR	GCT
O'Sullivan Coyne et al[89]	Paclitaxel + nilotinib	$N = 3$ adults, recurrent	66% (2 of 3 pts)	> 5 y for responding pts	NR	GCT

[a]Front line for patients with de novo metastatic and for those with recurrence after curative surgery.
[b]Heterogenous patient population across different trials/series precludes conclusive comparison, as some of the patients received treatment after cytoreductive surgery with or without residual disease, whereas others did not undergo surgery at all.
BEP: bleomycin, etoposide, cisplatin; CAP: cyclophosphamide, doxorubicin, cisplatin; CBR: clinical benefit rate; CP: carboplatin, paclitaxel; GCT: granulosa cell tumor; mOS, median overall survival; mPFS: median progression-free survival; NR: not reached; pts: patients; PVB: cisplatin, vinblastine, bleomycin; SCST: sex cord–stromal cell tumor; SD: stable disease.

In another retrospective review in patients with advanced GCT, BEP resulted in 71% (7 of 10) overall response rate (ORR) and 11.2 months mPFS, compared with 37% (14 of 37) ORR and 7.2 months mPFS for taxane-based regimens. However, none of the differences were statistically significant, possibly due to the small sample size.[62] Furthermore, superior ORR was reported following platinum-containing regimens compared with nonplatinum regimens (54% (7 of 13) vs 18% (3 of 17), respectively).[63] A prospective single-arm study where patients with de novo metastatic or recurrent GCT were treated with BEP reported an ORR of 90% (18 of 20) and PFS and OS of 25 and 46 months, respectively.[64]

Single-agent paclitaxel has been historically used as a second-line therapy in a weekly or once every 3 weeks treatment schedule. In a nonrandomized, single-arm phase II trial that included patients with metastatic progressive sex cord–stromal ovarian tumor (both GCT and non-GCT histologies) who failed one line of therapy, patients received paclitaxel 175 mg/m^2 once every 3 weeks. Among the 31 women treated, the response rate was 29% (complete response (CR) = 3.2%), and mPFS and mOS were 10 and 73.6 months, respectively.[65] The combination of carboplatin and paclitaxel is commonly used in GCT. However, a randomized phase II trial comparing paclitaxel and carboplatin (PC) treatment with BEP therapy in patients with advanced ovarian SCST (NCT01042522) reportedly closed for futility after interim analysis failed to prove noninferiority of PC compared with BEP. Outcome analysis of 63 accrued patients, 87% of whom had GCTs, 31 treated with PC and 32 treated with BEP, demonstrated the occurrence of more PFS events in the PC arm compared with the BEP arm (21 vs 16, respectively). As expected, PC had a more favorable side effect profile.[66] Clinical practice guidelines from the European Society for Medical Oncology (ESMO) suggest using BEP as the first-line option for advanced disease. In older patients, a combination of carboplatin and paclitaxel may be better tolerated.[67] Retrospective analysis data suggest a lower response rate in patients with relapsed disease treated with taxane-based regimens compared with BEP.[58] For patients with relapse or progression after first-line BEP therapy, paclitaxel, liposomal doxorubicin, capecitabine, or hormonal therapy may be used.[67]

Endocrine Therapy

Due to the presence of hormonal receptor expression in GCT, and the proposed role of the oncogenic FOXL2 mutation in steroidogenesis through upregulation of aromatase activity, a variety of endocrine-targeted approaches have been used, with varying success rates.[57] Agents used in advanced disease include aromatase inhibitors, selective ER modulators, gonadotropin hormone-releasing hormone (GnRH) agonists, antagonists, and progestins.[68] Among these, aromatase inhibitors have been the most studied and found to be the most efficacious. A systematic review of case series and case reports showed that anastrozole and letrozole produced superior activity compared with the other endocrine therapies.[69] Alhilli and colleagues[70] reported a response rate of 100% for aromatase inhibitors in their review of published literature in the treatment of GCT. All of the patients were surgically or medically postmenopausal. GnRH agonist leuprolide was reported to produce partial responses in two of five evaluable patients with relapsed and/or refractory GCT.[71]

A separate retrospective rare tumor registry study of first-time exposure to leuprolide acetate in recurrent GCTs ($n = 62$) demonstrated a 6-month clinical benefit rate of 66% and mPFS not statistically different when compared with chemotherapy.[72] Likewise, scattered case reports have noted some activity for GnRH agonist, tamoxifen alone, a combination of both, or tamoxifen with megestrol in alternating schedule.[73–76] The PARAGON/ANZGOG 0903 trial is the largest prospective study to examine the efficacy of endocrine therapy with an aromatase inhibitor in the treatment of recurrent ER- and/or PR-positive GCT. In this single-arm trial, postmenopausal women with recurrent or metastatic GCT or SCST received anastrozole 1 mg daily. The study reported a disease control rate (partial response (PR)+ stable disease (SD)) approaching 80%, with a median PFS of 8.6 months.[77] Delayed tumor regressions were noted in some patients occurring beyond 12 weeks of treatment. A case report described a response to a combination of the steroidal anti-inflammatory exemestane with the mTOR inhibitor everolimus in a female patient who was no longer responding to letrozole monotherapy.[78]

Targeted Therapy and Future Perspectives

Given the high expression of VEGF in most SCST and preclinical evidence supporting the use of antiangiogenic agents, bevacizumab has been investigated as a potential treatment for SCST, either alone or in combination with chemotherapy.[79] However, in a nonrandomized phase II trial of relapsed or progressive SCST, the majority of which were GCT, the response rate was only 17%, and mPFS was 9.3 months.[80] In another randomized trial of SCST, including mainly GCT, the addition of bevacizumab to weekly paclitaxel beyond the platinum-based first line did not improve PFS at 6 months, though response rates were higher with the combination.[81]

Although immunotherapy has not been extensively tested in GCT, a prospective phase II basket trial enrolled five heavily pretreated GCT patients (four adults, one juvenile) with pembrolizumab, an anti–PD-1 checkpoint inhibitor; no tumor regression was observed, but two patients with adult-type GCT achieved stable disease lasting more than 12 months. Four patients had no detectable PD-L1 expression.[82] However, as discussed earlier, GCT does not appear to exhibit a biomarker of response to immune checkpoint blockade.[34] To investigate GCT tumor microenvironment (TME) further, Khlebus et al[83] demonstrated statistically significant depletion of cancer-associated

fibroblasts (CAFs) in recurrent GCT TME based on differential gene expression analysis, suggesting that recurrent GCT may have an advantage in responding to immunotherapy. Moreover, Pierini et al[84] identified tumor-infiltrating lymphocytes (TILs) as the main immune population within GCT. Ex vivo expansion of TILs from 11 GCT patients was found to be sufficient to react against autologous tumors in 100% of patients and against FOXL2 peptides in 57% of patients in vitro. Consequently, the team demonstrated a promising approach by exploiting the FOXL2 mutation to create a plasmid DNA vaccine, which resulted in reduced tumor growth and tumor growth control in FOXL2-expressing tumors in a mouse model. Additionally, coadministration with anti–PD-L1 immune checkpoint inhibitors enhanced the antitumor activity of the DNA vaccine in mice.[84]

A combination therapy approach for GCT has been explored in recent studies. One such approach is the combination of temozolomide with the base excision repair inhibitor TRC102 (methoxyamine), which resulted in two patients with adult-type GCT experiencing a partial response lasting more than 12 months.[85]In addition, tyrosine kinase inhibitors have shown promising results in preclinical models when used in combination with mTOR inhibitors or taxane chemotherapy.[86,87] A case report demonstrated the efficacy of imatinib in GCT treatment.[88] Furthermore, a prospective phase I trial in solid tumors reported a long-lasting partial response (over 5 years) to treatment with paclitaxel and nilotinib in two adult-type GCT patients who had previously progressed on taxanes. Unfortunately, a third patient with juvenile GCT did not respond to the same regimen.[67,89]

Upregulation of inhibitor of apoptotic proteins (IAP), particularly XIAP, was demonstrated in GCT cell lines and patient-derived samples compared with normal ovarian cells in vitro.[90] Based on this, SMAC (second mitochondria-derived activator of caspase) mimetic able to block IAPs was shown to induce apoptosis in GCT cell lines in vitro.[90,91]

The role of c-Jun N-terminal kinase (JNK) pathway in the proliferation of malignant granulosa cells has raised interest in targeting this pathway in GCT, and in vivo inhibition of JNK resulted in significant growth inhibition of patient-derived GCT xenografts.[92] Although EGFR is thought to play a minimal role in GCT tumorigenesis,[93] cell line data suggest a role for the fibroblast growth factor 1 (FGF1) in mediating GCT cells' resistance to platinum chemotherapy, opening up future novel combinatorial treatment options in clinic.[94]

PATIENT PERSPECTIVE

Patient involvement and education about treatment options are important in rare cancer diagnosis. Many local, national, and international support groups exist to help and educate patients. Groups such as the National Ovarian Cancer Coalition (NOCC) (ovarian.org) and Ovarcome (ovarcome.org) meet online via Zoom monthly. These organizations offer many support services. Although most of these groups are generic ovarian cancer groups, they can still be beneficial for patients with GCT. Even though the types of cancer the women have may be different, there are many similarities in treatment paths. There is one private group specifically for GCT on Facebook called "GCT Survivor Sisters!" comprising 1,769 women from around the world, sharing the latest research from around the world. Women also share their personal stories about treatment and side effects.

There are many ways to get more involved in the ovarian cancer community at the local and national level. Local ovarian cancer groups are always looking for volunteers. Nationally, the Ovarian Cancer Research Alliance (OCRA), ocrahope.org, provides opportunities for women to get involved in supporting other survivors and research through multiple programs such as Survivors Teaching Students, Peer to Peer, and Advocacy. A multitude of opportunities exist for women of all ages, stages of disease and desired level of involvement. Additionally, there are two groups that have dedicated research specifically for GCTs: the Granulosa Cell Tumour Research Foundation (GCTRF) in Canada and Hudson Institute of Medical Research in Australia. GCTRF funds research grants annually. The list of its grantees and their research can be found at gctrf.org, where people can also find information about GCT. The work of the Hudson Institute can be found at hudson.org.au/disease/cancer/ovarian-cancer. Both GCTRF and Hudson Institute partner with the members of the GCT Survivor Sisters! Facebook group to provide educational programs, and the Facebook community, in turn, supports these groups by providing tissue samples that are critical for research.

CONCLUSION

For patients with recurrent or advanced GCT, a multidisciplinary approach incorporating debulking or cytoreduction surgery followed by systemic therapy is recommended. The initial option for systemic therapy may include a multiagent regimen, BEP being the most validated. Endocrine therapy can be used as a chemotherapy-sparing option in patients who do not wish to receive cytotoxic chemotherapy. Tumors should be sent for molecular analysis to confirm the diagnosis and aid in the selection of appropriate novel targeted therapy. Preclinical models such as organoids, cell lines, and patient-derived xenograft models can be used for drug screening to identify novel targeted therapeutics in this disease. Additionally, converting the tumor immune microenvironment from "cold" to "hot" may be a potential novel therapeutics approach by targeting FOXL2 protein to increase TILs into TME or targeting recurrent GCT, which TME seems less immunosuppressive due to fewer CAFs, allowing for

future combinations with immune checkpoint inhibitors. Nonetheless, larger clinical trials are needed, and enrollment should be strongly encouraged, irrespective of stage or line of therapy.

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