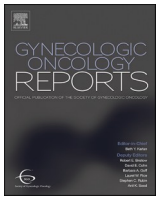
Gynecologic Oncology Reports 56 (2024) 101502

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor



Treatment of recurrent ovarian germ cell tumours: Is there a role for immune checkpoint inhibitors?

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A B S T R A C T

Ovarian germ cell tumours predominantly affect young women and have an excellent prognosis. While most contemporary papers concentrate on reducing treatment morbidity and preserving fertility, some women still succumb to refractory or recurrent OGCTs. Despite the significant impact of immune checkpoint inhibitors (ICIs) on many tumors, no case of a chemo-resistant ovarian germ cell tumour successfully treated with immunotherapy has been reported. In testicular cancer, only a few cases of partial response or stable disease to ICIs have been described. PD-L1 expression does not predict response, but microsatellite instability status may serve as a potential biomarker. MSI testing should be performed on a recurrent tumour sample as MSI status may evolve during treatment.

1. Ovarian germ cell tumour: Definition and epidemiology

Ovarian germ cell tumours (OGCTs) typically affect young women in their late teens or early twenties and represent only 5 % of all ovarian malignancies. The 2020 World Health Organization classification is comprised of dysgerminoma, yolk sac tumour, embryonal carcinoma, non-gestational choriocarcinoma, mixed germ cell tumour, and teratoma (mature, immature and monodermal) (McCluggage et al., 2020) Dysgerminoma is the most common malignant OGCT, and a small percentage of these tumours are associated with gonadoblastomas and gonadal dysgenesis or the presence of a Y chromososome (Chi et al., 2017). Yolk sac tumours (formerly known as endodermal sinus tumours) are the second most common OGCTs. Embryonal carcinomas are rare in the ovary, but are more common in testicular cancers (Kurman and Norris, 1977). Primary non-gestational ovarian choriocarcinomas are typically more aggressive than gestational choriocarcinomas (Rao et al., 2015). Mixed germ cell tumours contain two or more different types of germ cell neoplasms, the most frequent combination being dysgerminoma and yolk sac tumour. Immature teratomas represent 3 % of ovarian teratomas, contain immature neural tissue and are considered malignant. Monodermal teratomas are composed of one type of tissue, such as thyroid (struma ovarii), carcinoid tumour or primitive neuroectodermal tumours. (Chi et al., 2017).

2. Standard of care

Treatment algorithms depend on the type of tumour and the age of the patient. The standard surgical approach for pre-menopausal woman and children includes peritoneal cytology, ipsilateral oophorectomy, omental biopsy, and depending on tumour factors and society recommendations, either palpation of the pelvic and paraaortic lymph nodes and excision of abnormal nodes, or sampling of the lymph nodes if no suspicious node can be detected. (Network, 2024; Sessa et al., 2020) Some patients will require adjuvant chemotherapy.

The evolution of chemotherapy for ovarian germ cell tumours has always followed the advances made in the treatment of testicular cancer. One of the first treatments established in the 1970 s was vincristine, actinomycin-D, and cyclophosphamide (VAC), but less than 50 % of advanced stage ovarian germ cell tumours patient had long-term responses. (Slayton et al., 1985) Once cisplatin was introduced and the combination of vinblastine, bleomycin, and cisplatin (PVB) was developed for testicular cancer, studies determined its superiority in OGCTs. (Williams et al., 1989) Further studies in testicular cancer proved that etoposide was equivalent to vinblastine, with a more favorable side-effect profile. This established the bleomycin, etoposide and cisplatin (BEP) regimen. (Williams et al., 1987; Gershenson et al., 1990) The majority of patients are cured with surgery and chemotherapy, but some patients have persistent or recurrent disease. They accounted for 42 patients out of 160 in a case study from MD Anderson, and less than 50 % of these patients could be salvaged with subsequent therapy. (Messing et al., 1992).

3. Outcomes and management of residual or recurrent disease

The large majority of patients are cured with surgery and platinum-based chemotherapy: 17.8 % of OGCTs recur, usually within 24 months,

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https://doi.org/10.1016/j.gore.2024.101502
Received 28 July 2024; Received in revised form 1 September 2024; Accepted 7 September 2024
Available online 19 September 2024
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and are fatal in 12 %-25 % of cases. (Mangili et al., 2011; Gershenson, 2007) Like in testicular cancer, they are categorized as platinum-resistant (less than 4–6 weeks after platinum-based chemotherapy completion) or sensitive (beyond 6 weeks). No standard of care has been established for the patients presenting with a recurrence. Recurrences can be treated with high-dose chemotherapy and stem cell transplant, or paclitaxel, ifosfamide and cisplatin (TIP). High-dose chemotherapy and stem cell transplant has a reported response rate of 53 % for relapsed OGCTs, while TIP has been associated with a 37 % response rate. (Network, 2024; Reddy Ammakkanavar et al., 2015; Kurobe et al., 2015) New agents, such as immune checkpoint inhibitors, are currently studied.

4. Potential for immunotherapy

Over the past few years, many strategies have been developed to modulate the immune system in an effort to optimize anti-tumour immunity and its oncolytic properties. The immune system relies on various immune checkpoints to maintain self-tolerance and protect tissue from damage after activation of the immune response to pathogens. Programmed cell death 1 (PD-1) and cytotoxic T-lymphocyte–associated protein-4 (CTLA-4) are molecules implicated in immune checkpoint regulation. PD-1 is a receptor present on activated T cells, while PD-L1 is expressed on the surfaces of various cancer cells. (Sharma and Allison, 2015) CTLA-4 mediates immunosuppression by indirectly diminishing signaling through the co-stimulatory receptor CD28, which increases the activation threshold of T cells, reduces immune responses to weak antigens such as tumour antigens (Seidel et al., 2018) and results in results in tumour rejection (Tang et al., 2018). There is currently very little evidence of activity of immune checkpoint inhibitors (ICI) on ovarian germ cell tumours.

However, gestational choriocarcinomas, which have been shown to share common pathway with non-gestational choriocarcinomas, have been shown to respond to immune checkpoints inhibitors (Huang et al., 2017; Veras et al., 2017; Ghorani et al., 2017). PD-L1 is expressed in premalignant and malignant trophoblasts, and targeting of this pathway is currently explored as first-line and second-line treatment for gestational choriocarciomas. (You et al., 2020).

Expression of PD-L1 in ovarian germ cell tumours is largely undetermined. Alwosaibai et al. have found in their cohort of 34 ovarian germ cell tumours that 100 % of non-gestational choriocarcinoma and 90 % of the dysgerminoma expressed PD-L1, while 36 % of the immature teratoma and 0 % of the yolk sac tumours expressed the protein. The choriocarcinoma and dysgerminoma components of the five mixed germ cell tumours were PD-L1 positive. (Alwosaibai et al., 2024) Given these findings, the idea to test the response of ovarian germ tumours to immunotherapy has emerged. So far, only two cases have been reported.

In a small open-label, phase II clinical trial in which patients with advanced metastatic germ cell tumours were treated with pembrolizumab, two female patients were enrolled (Tsimberidou et al., 2021). One patient had a mixed germ cell tumour, comprised of an immature teratoma, grade 2, yolk sac tumour and embryonal carcinoma, while the second patient had a yolk sac tumour. The mixed germ cell tumour was found to be PD-L1 negative, without tumour-infiltrating lymphocytes. The yolk sac tumour was not tested for PD-L1. Both patients experienced progressive disease on pembrolizumab, one after 4 months, and the second after 2.5 months. (Table 1).

Interestingly, one case of extragonadal non-gestational choriocarcinoma in a female patient, treated with pembrolizumab, has been reported. The tumour was PD-L1 positive. The patient was found to have hyperprogression after 3 cycles of immunotherapy, and she passed away 10 weeks after starting pembrolizumab. (Kazemi et al., 2022).

Ovarian germ cell tumours are believed to be microsatellite-stable (MSS). In a case series that included three ovarian germ cell tumours, all cases were MSS. (Montella et al., 2023) Ten patients with ovarian yolk sac tumours were also found to have MSS tumours. (Hodroj et al., 2021) However, the samples tested for these analyses were from the original tumours, and not relapsed tumours, which may impact MSI status, as previously shown in testicular tumours. (Honecker et al., 2009).

5. Lessons learned from testicular cancer

Recurrent or resistant testicular germ cell tumours are much more common than their ovarian counterparts, and most studies on immunotherapy in germ cell tumours have predominantly included testicular cancers. Testicular germ cell tumours (TGCT) are divided into pure seminoma and non-seminomatous germ cell tumours (NSGCT). Approximately 70–80 % of patients with disseminated disease can be cured with cisplatin-based chemotherapy.(2) Second or third-line chemotherapy with high-dose chemotherapy (HDCT) and autologous peripheral- blood stem-cell transplant offers cure in a large proportion of patients treated with this salvage regimen with a 2-year progression-free survival (PFS) of 60 % and 2-year overall survival (OS) of 66 % (Adra et al., 2017). Long-term complete remission is found in 40–50 % of relapsed patients after first salvage treatment with second-line chemotherapy or high-dose chemotherapy followed by autologous stem cell transplant.

- Anti-PD-L1

Expression of PD-L1 was significantly higher in testicular GCTs in comparison to normal testicular tissue. PD-L1 expression was found in 73 % of all seminomas and in 64 % of all non-seminomas. (Fankhauser et al., 2015) The highest level of PD-L1 is seen in choriocarcinoma, with decreasing positivity in embryonal carcinoma, teratoma, yolk sac tumour and seminoma. PD-L1 expression in TGCT is associated with poor prognostic features, including more than three metastatic sites, increased serum tumour markers and visceral metastases, while patients with low PD-L1 expression had significantly better PFS and OS. (Cierna et al., 2016). Unfortunately, this information has yet to translate into therapeutic benefit.

A Phase II study of avelumab (PD-L1 antagonist) was performed in 8 patients with refractory TGCT (NCT03403777). During a median follow-up period of 2.6 months (range: 0.3—14.4), 7 (87.5 %) patients experienced disease progression, and 6 patients (80.0 %) died. Twelve-week PFS was 0 %, median PFS was 1.4 months, 95 %CI (0.9 – 1.4) and median OS was 2.7 months, 95 % CI (1.0 – 3.3). No objective response was observed. (Mego et al., 2019) (Table 2).

Another open label, randomized, Phase II study, APACHE

Table 1
Summary of studies reporting on ICI in OGCTs.

Author; year; country	Study design; Sample size	Patient population	Treatment	Histology (female patients)	Response
Tsimberidou et al. 2021. USA	Open label, phase II	Advanced metastatic GCT (2 female patients, 10 male patients)	Pembrolizumab	- Mixed germ cell tumour (Immature teratoma, yolk sac tumour and embryonal carcinoma, PD-L1 negative) - Yolk sac tumour (PD-L1 unknown)	- PD (4 months) - PD (2.5 months)

Abbreviations: PD (Progressive disease).

Table 2
Summary of studies reporting on ICI in testicular GCTs.

Author; year; country	Study design; Sample size	Patient population	Treatment	Histology	Response
Mego et al. 2019	Open label, phase II	Refractory TCGT	Avelumab	Nonseminoma (100 %)	Median PFS 1.4 months
Slovakia	N=8			PD-L1 status unknown MSI status unknown	Median OS 2.7 months No objective response
Raggi et al. 2018	Open label, randomized, phase II	Advanced and relapsed GCT	Durvalumab vsDurvalumab + tremelimumab	Seminoma (9.1 %), nonseminoma (90.9 %)	PR in 1 patient (in arm B, 9.1 %. PD-L1 negative and MSS)
Italy and USA	N=22			Gondal (72.7 %), extragonadal (17.3 %)	SD in 1 patient (in arm B, 9.1 %)
				2 patients noted to be MSI	Progression occurred regardless of PD-L1 expression
				PD-L1 status for the cohort is unavailable	Hyperprogression observed in 12 cases
Funt et al. 2023	Single arm, phase II	Relapsed/ refractory GCT	Durvalumab and tremelimumab	Seminoma (14 %), nonseminoma (86 %)	16w PFS: 13.8 %
USA	N=29			13 patients were PD-L1 negative, 7 patients PD-L1 high, 9 unknown	Median PFS 1.4 months Median OS: 7.3 months 1 patient has PR and 2 patients had reduction of tumour < 30 %.
Adra et al. 2018	Single arm, phase II	Refractory GCT	Pembrolizumab	Nonseminoma (100 %)	SD (but rising AFP) in 2 patients for 28 and 19 weeks. PD-L1 negative.
USA	N=12			PD-L1 high in 2 patients	
Tsimberidou et al. 2021	Open label, phase II	Advanced metastatic GCT (2 female patients, 10 male patients)	Pembrolizumab	Nonseminoma or non-dysgerminoma (100 %)	SD in 3 patients for 10.9 months, 5.5 months, 4.5 months (PD-L1 negative in 2 patients, unknown for one)
USA	N=12			PD-L1 high in 2 patients, negative in 6, unknown in 4	
Kawai et al. 2021	Case Report	Refractory GCT	Pembrolizumab	Seminoma in primary tumour, mixed in lymph node metastasis (PD-L1 positive, MSI-High after chemotherapy, MSS prior to chemotherapy)	CR for 6 months
Japan	N=1				
Shah et al. 2017	Case report	Chemo-naïve GCT	Nivolumab	Embryonal cell carcinoma (PD-L1 low positive)	PR after 1 dose, changed to BEP chemotherapy
USA	N=1				
Zschäbitz et al. 2017	Case series	Refractory GCT	Nivolumab or Pembrolizumab	Nonseminoma (100 %)	PR in 3 patients, 2 of which has PD-L1 high expression
Germany	N=7			PD-L1 high in 4 patients	
Chi et al. 2017	Case report	Refractory GCT	Nivolumab	Choriocarcinoma (PD-L1 unknown)	PR
USA	N=1				
Nadal et al. 2018	Phase I basket trial N=5 patients with GCT	GCT	Cabozantinib + nivolumab with or without ipilimumab	Unknown	PD

Abbreviations: PFS (Progression-free survival); OS (Overall survival); CR (Complete response), PR (Partial response); SD (Stable disease); PD (Progressive disease).

(NCT03081923) was investigating the anti-PD-L1 durvalumab, alone (arm A) or in combination with tremelimumab (arm B), an anti-CTLA4 monoclonal antibody, in patients with advanced and relapsed GCT. In arm A, 100 % of pts had disease progression (PD), in arm B, 2 responses were noted (22.2 %, 1 partial response in seminoma and 1 stable disease with tumour marker reduction in non-seminoma). PD occurred in both arms regardless of PD-L1 expression. (Raggi et al., 2018) A single-arm, Phase II study assessing the combination of durvalumab and tremelimumab in relapsed/refractory GCT (NCT03158064) was presented but not published, only one patient out of 29 had a durable partial response. (Funt et al., 2023).

- Anti-PD-1

The first Phase II trial of pembrolizumab in patients with platinum-refractory GCT showed no clinical benefit for pembrolizumab, an anti-PD-1 antibody (NCT02499952). This study enrolled 12 men with non-seminomatous testicular tumours irrespective of their PD-L1 status. Only two patients had PD-L1-positive tumours. Ten of 12 patients progressed (including those being PD-L1 positive) and only two, who had negative PD-L1 staining, had a mixed response with radiographic stability but rising AFP. (Adra et al., 2018).

A second phase II trial of pembrolizumab, of which the outcomes of the 2 female patients were reported above, also included 10 male patients. Overall, three patients had radiographic stable disease that lasted for 10.9 months, 5.5 months, and 4.5 months, respectively. No objective response was noted. Two of the patients with stable disease were found to be PD-L1 negative, the third patient was not tested. (Tsimberidou et al., 2021).

One case reported complete response to pembrolizumab in a patient with pure seminoma, who was found to show microsatellite instability (MSI-High); his tumour was MSI-low prior to initial treatment, but developed into a MSI-High tumour after four chemotherapy regimens. (Kawai et al., 2021) MSI-high is rare in germ cell tumours, but several studies suggested the incidence is higher in chemo-refractory TGCT compared to the chemo-naïve primary tumour. (Honecker et al., 2009).

One man with metastatic NSGCT (embryonal cell carcinoma) with cervical and retroperitoneal nodal involvement, was treated with a single dose of nivolumab (anti-PD-1), as it was first believed to be metastatic melanoma. He had a 33 % regression in tumour volume based on the RECIST criteria and 49 % reduction by immune-related response criteria. The treatment was switched to bleomycin, etoposide and cisplatin for three cycles with a complete radiographic response. (Shah et al., 2016).

In a case series, seven male patients with platinum-refractory NSGCT were treated with an anti-PD-1 therapy (nivolumab or pembrolizumab). Four patients had rapid disease progression and died shortly after starting treatment. Three others continued to receive therapy for at least 6 months: among them, one patient (embryonal NSGCT) achieved a partial radiographic response, one (yolk sac tumour and mature teratoma) had stable disease and one (yolk sac tumour and immature teratoma) had a mixed response followed by progression. There seemed to

be no association between the PD-L1 staining and response. (Zschäbitz et al., 2017).

A patient with metastatic retroperitoneal choriocarcinoma was shown to have a progressive disease following multiple lines of chemotherapy and tandem autologous stem cell transplantation. He then received nivolumab for 14 months with a resultant partial radiographic response and decline of ß-HCG. He was then followed with watchful observation. (Chi and Schweizer, 2017).

In a recent phase I basket trial assessing cabozantinib plus nivolumab with or without ipilimumab (anti-CTLA4) in genitourinary cancers, no responses were seen in five GCT patients who were included. (Nadal et al., 2018).

6. Conclusion

While malignant OGCTs typically have an excellent prognosis, a subset of recurrent tumors remains resistant to current therapies and ultimately fatal. There are no successful case reports of OGCTs treated with ICIs. In TGCTs, small clinical trials have not demonstrated significant benefits from ICIs, though some patients have shown partial responses or stable disease. PD-L1 expression does not predict response, but MSI status may serve as a potential biomarker for immunotherapy response. The role of tumour mutational burden and tumour infiltrating lymphocytes also remains to be studied as a potential biomarker for response. Clinically, MSI testing should be performed on a recurrent tumour sample as MSI status may evolve during treatment.

This suggests that a subset of chemo-resistant germ cell tumors might benefit from immunotherapy. The inclusion of OGCTs in clinical trials should therefore be encouraged.

CRediT authorship contribution statement

Laurence Bernard: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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