First-line chemotherapy in low-grade serous ovarian cancer: a single center retrospective cohort

C. Della Pepa[1], P. Gargiulo[1], M. Di Napoli[1], S. Cecere[1], S. Losito[1]

Abstract

Background Low-grade serous ovarian carcinoma (LGSOC) is a rare histotype of epithelial ovarian carcinoma (EOC) that is associated with a high rate of KRAS and BRAF mutations, young age at diagnosis, indolent behavior, and resistance to standard platinum-based chemotherapy. Here we report details of advanced LGSOC cases treated with primary chemotherapy at our institution from 2009 to 2014.

Patients and methods We retrospectively reviewed the medical records of 17 patients with histology-confirmed LGSOC, 6 of whom had measurable disease on computed tomographic scan when receiving first-line chemotherapy and were therefore evaluable for response. Response to platinum-based chemotherapy was documented using RECIST criteria and CA125 levels.

Results One patient had a complete response, 2 had a partial response, 1 had stable disease and 2 patients progressed, resulting in an overall response rate of 50%. Of note was that 3 patients who partially responded to chemotherapy were started on tamoxifen maintenance and achieved good progression-free survival (up to 5 years).

Conclusions Despite literature suggesting that LGSOC is much less sensitive to platinum agents than high-grade serous ovarian carcinoma, our case series suggests that the response rate may be higher than previously reported and that tamoxifen may have a role as maintenance treatment.

Key words: chemotherapy, low-grade serous ovarian carcinoma, platinum agents resistance, tamoxifen

Introduction

Low-grade serous ovarian carcinoma (LGSOC) is a rare histotype of ovarian cancer, accounting for 5–10% of all ovarian tumors [1]. Compared to the high-grade subtype (HGSOC), LGSOC is characterized by younger age at diagnosis and indolent behavior. In addition, response to chemotherapy seems to be very poor, although most data refer to second-line setting [2, 3].

The clinical differences between LGSOC and HGSOC relate to different genetic aberrations: HGSOC is associated with genetic instability and early p53 mutation, while LGSOC seems to develop from serous borderline tumor (SBLT) via alteration of the RAS-signaling pattern and abnormal activation of the MAPK/ERK pathway [4].

Available data on LGSOC come largely from retrospective studies because the disease is relatively rate and histological classification has been ambiguous, making prospective studies difficult. The only prospective data available come from a phase II trial evaluating selumetinib in the recurrent setting [5]. The results were so promising that a phase III trial that is currently investigating use of a MEK inhibitor is underway (MILO study; clinicaltrials.gov identifier: NCT 01849874).

On the basis of American data showing extreme chemo-resistance of LGSOC, even in the first-line setting, we retrospectively analyzed cases of advanced LGSOC treated with first-line platinum-based chemotherapy at our institution.

Methods

Data were retrospectively collected from the medical records of patients diagnosed with LGSOC. Diagnosis was confirmed by review of specimens by a pathologist. Seventeen eligible patients were identified, 7 of whom had measurable disease on computed tomographic (CT) scanning when receiving first-line platinum-based chemotherapy. One patient wasn't evaluable for response due to lack of clinical data

[1]Uro-Gynecological Department and Surgical Pathology Unit, National Cancer Institute "G. Pascale" Foundation, Naples, Italy.

Correspondence to: Dr. Chiara Della Pepa, Dipartimento Uro-ginecologico e Unità di Chirurgia, Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Via Mariano Semmola 52, 80131 Napoli, Italy.
Phone: +39 389 5530745 – Fax: +39 081 5903861
E-mail: chiaradellapepa@hotmail.it

CANCER BREAKING NEWS 2015;3(1):27-30

and therefore the remaining 6 cases were included in this analysis. Chemotherapy regimen was conventional 3-weekly carboplatin-paclitaxel 175 mg/mq in 3 patients, carboplatin-paclitaxel as the MITO 7 trial protocol [6] in 1 patient, and 3 patients received carboplatin monotherapy due to poor clinical condition. Response to chemotherapy was assessed using RECIST criteria [7] and CA125 [8].

Results

All patients had histologically-confirmed LGSOC (G1 serous ovarian cancer) diagnosed between October 2009 and July 2013. Age at diagnosis was 36–69 years, 4 patients had stage IIIC disease, 1 patient had stage IV disease (cytology-confirmed malignant pleural effusion) according to International Federation of Gynecology and Obstetrics (FIGO) staging, and the remaining patient had an invasive recurrence of SBLT. All but 2 patients had a normal body mass index, 5/6 patients presented with significant CA125 elevation at diagnosis and 3 had ascites. Patients characteristics are summarized in Table 1.

Three of the six patients responded to first-line platinum-based chemotherapy according to RECIST and CA125 criteria: one patient had a complete response (CR), two had a partial response (PR), one had stable disease (SD) and two patients had progressive disease (PD), for an overall response rate (ORR) of 50%. Three patients underwent interval debulking surgery (IDS), which achieved residual tumor of <1 cm in two patients.

Time to second-line treatment was quite variable: the two patients who progressed on platinum were heavily symptomatic and immediately received a new regimen; the patient who achieved a CR quickly progressed after completion of 6 cycles and required a second-line treatment after 5 months; the patient with SD and the two patients who partially responded had a significant progression-free interval (8 months, 2 and 5 years, respectively). Of note, all three of these patients received tamoxifen as maintenance after chemotherapy discontinuation. Patient outcomes are summarized in Table 2.

Discussion

In our retrospective analysis of LGSOC patients receiving platinum-based chemotherapy, the ORR was 50% which is higher than expected. In a similar retrospective cohort of 25 patients with advanced LGSOC, Schmeler et al. [9] reported CR in 1 patient (4%), SD in 21 patients (84%), PD in 2 patients (8%); 10 patients (40%) had a >50% reduction in CA125 levels. Another paper from the same

Table 1. Patient characteristics

Pt	Age (years)	Stage	BMI (kg/m^2)	Measurable disease by RECIST	CA125 elevation	Ascites
1	36	IIIC	27.3	yes	yes	no
2	69	IV	21.2	yes	yes	no
3	40	IIIC	18.4	yes	yes	yes
4	44	Inv Rec of SBLT	24.1	yes	no	no
5	57	IIIC	21.3	yes	yes	yes
6	53	IIIC	22.8	yes	yes	yes

BMI: body mass index; Inv Rec of SBLT: invasive recurrence of serous borderline tumor; pt: patient.

Table 2. Response to first-line platinum-based chemotherapy

Pt	Chemotherapy regimen	Best response RECIST	Best response CA125	IDS	RT after IDS	Time to second-line CHT	Tamoxifen maintenance
1	CBCDA-PTX q1w (MITO 7)	SD	SD	yes	< 1 cm	2 years	yes
2	CBCDA-PTX q3w	CR	PR	yes	0	5 months	no
3	CBCDA q3w	PD	PR	no	–	0 months	no
4	CBCDA-PTX q3w	PR	NA	yes	> 1 cm	5 years	yes (3 years)
5	CBCDA-PTX q3w	PR	PR	no	–	8 months	yes (6 months)
6	CBCDA q3w	PD	PD	no	–	0 months	no

CBCDA: carboplatin; CHT: chemotherapy; CR: complete response; IDS: interval debulking surgery; MITO 7: MITO 7 study [8]; NA: not applicable; PD: progressive disease; PR: partial response; pt: patient; PTX: paclitaxel; q1w: weekly; q3w: 3 weekly; RT: residual tumor; SD: stable disease.

group focused on 53 cases of primary peritoneal low-grade serous carcinoma (PPLGSC) [10]. Strong chemo-resistance was documented, with 72% of patients having persistent or progressive disease at the completion of primary treatment. In the recurrent setting, chemo-sensitivity data are equally disappointing. In a study of 58 patients who received 108 chemotherapy regimens by Gershenson et al., the ORR was just 3.7% [11]. In the light of such data, the recent Gynecologic Cancer InterGroup (GCIG) Consensus for LGSOC has warned gynecological oncologists about the use of neoadjuvant chemotherapy in LGSOC patients [12].

Although our retrospective cohort is small in comparison to previous studies, all the histology samples were reviewed and the aim of the analysis was to provide some preliminary data and to highlight that some patients with LGSOC do respond to platinum-based chemotherapy.

Both in our cohort and in previous reports the ORR in LGSOC patients is considerably lower than the 70−80% observed for first-line therapy in the HGSOC population [13]. Potential reasons for this may include the low mitotic index and abundance of calcified disease deposits in LGSOC, but the most likely explanations related to genetic factors and the different carcinogenesis pathways of these subtypes of ovarian cancer. The high rate of BRAF and KRAS mutations in SBLTs and LGSOCs has been highlighted in several papers [14, 15], but much is still unclear about the clinical significance of such mutations in terms of both prognostic and therapeutic value. It seems that tumors harboring a BRAF mutation have a better outcome and are unlikely to require chemotherapy [16] but no data are available about KRAS/BRAF mutation (the mutations are mutually exclusive) or MAPK/ERK up-regulation and sensitivity to platinum. The next step in understanding how to treat LGSOC patients might be exploring the genetic profile, finding relationships between DNA aberrations and sensitivity to chemotherapy/target agents and to personalize therapy as much as possible.

Interestingly, the 3 patients who had a relatively long progression-free interval in our analysis (8 months to 5 years) received tamoxifen as maintenance treatment. The activity of hormonal treatment in LGSOC has been already reported in the recurrent setting [17]; in a cohort of 64 patients the ORR was 9% and prolonged SD was observed for 62% of the 89 hormonal regimens. To the best of our knowledge there is no literature about giving tamoxifen as maintenance after platinum discontinuation in responders, but such an approach certainly deserves to be considered and further explored in larger cohorts.

Finally, it is worth mentioning studies of bevacizumab in combination with chemotherapy: in two cohorts of 13 and 15 patients with recurrent, heavily pretreated LGSOC [18, 19], the ORR was 39% and 40%, respectively. There are no data about first-line bevacizumab therapy in this subset of patients and, unfortunately, our analysis could not provide any data because the only patient who received bevacizumab plus carboplatin-paclitaxel was not evaluable for response. The addition of an antiangiogenic agent to the treatment of newly-diagnosed LGSOC patients (in combination with platinum-based chemotherapy and then as maintenance) should be subject of further research.

Conclusion

While acknowledging the small number of patients and the retrospective nature of our study, it does show that some patients with LGSOC do respond to platinum-based chemotherapy. In addition, interesting observations about the use of tamoxifen as maintenance therapy in LGSOC patients who partially respond to chemotherapy provide directions for future research. Further studies on larger cohorts are required to determine whether the ORR for first-line platinum chemotherapy may be higher than expected are also required.

References

1. Schmeler KM, Gershenson DM. Low-grade serous ovarian cancer: a unique disease. Curr Oncol Rep 2008;10(6):519-23.
2. Gershenson DM, Sun CC, Lu KH, et al. Clinical behavior of stage II-IV low-grade serous carcinoma of the ovary. Obstet Gynecol 2006;108(2):361-8.
3. Diaz-Padilla I, Malpica AL, Minig L, et al. Ovarian low-grade serous carcinoma: a comprehensive update. Gynecol Oncol 2012;126(2):279-85.
4. Singer G, Kurman RJ, Chang HW, et al. Diverse tumorigenic pathways in ovarian serous carcinoma. Am J Pathol 2002;160(4):1223-8.
5. Farley J, Brady WE, Vathipadiekal V, et al. Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: an open-label, single-arm, phase 2 study. Lancet Oncol 2013;14(2):134-40.
6. Pignata S, Scambia G, Katsaros D, et al. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 2014;15(4):396-405.
7. Eisenhauer EA, Therasseb P, Bogaertsc J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
8. Rustin GJS, Quinn M, Thigpen T, et al. Re: New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). J Natl Cancer Inst 2004;96(6):487-8.

9. Schmeler KM, Sun CC, Bodurka DC, et al. Neoadjuvant chemotherapy for low-grade serous carcinoma of the ovary or peritoneum. Gynecol Oncol 2008;108(3):510-4.
10. Schmeler KM, Sun CC, Malpica A, et al. Low-grade serous primary peritoneal carcinoma. Gynecol Oncol 2011;121(3):482-6.
11. Gershenson DM, Sun CC, Bodurka D, et al. Recurrent low-grade serous ovarian carcinoma is relatively chemoresistant. Gynecol Oncol 2009;114(1):48-52.
12. Gourley C, Farley J, Provencher DM, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for ovarian and primary peritoneal low-grade serous carcinomas. Int J Gynecol Cancer 2014;24(9 Suppl 3):S9-S13.
13. Ansquer Y, Leblanc E, Clough K, et al. Neoadjuvant chemotherapy for unresectable ovarian carcinoma: a French multicenter study. Cancer 2001;91(12):2329-34.
14. Singer G, Oldt R 3rd, Cohen Y, et al. Mutations in BRAF and KRAS characterize the development of low-grade ovarian serous carcinoma. J Natl Cancer Inst 2003;95(6):484-6.
15. Ho CL, Kurman RJ, Dehari R, et al. Mutations of BRAF and KRAS precede the development of ovarian serous borderline tumors. Cancer Res 2004;64(19):6915-8.
16. Grisham RN, Iyer G, Garg K, et al. BRAF mutation is associated with early stage disease and improved outcome in patients with low-grade serous ovarian cancer. Cancer 2013;119(3):548-54.
17. Gershenson DM, Sun CC, Iyer RB, et al. Hormonal therapy for recurrent low-grade serous carcinoma of the ovary or peritoneum. Gynecol Oncol 2012;125(3):661-6.
18. Schmeler KM, Tao X, Sun CC, et al. Encouraging responses with bevacizumab in recurrent low-grade serous ovarian cancer. ASCO 2010. Abstract e15503. Available from: http://meetinglibrary.asco.org/content/44366-74
19. Grisham RN, Iyer G, Sala E, et al. Bevacizumab shows activity in patients with low-grade serous ovarian and primary peritoneal cancer. Int J Gynecol Cancer 2014;24(6):1010-4.