Experiences from the German quality assurance program QS OVAR in partially platinum-sensitive recurrent ovarian cancer

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Abstract

Background The QS OVAR is a voluntary quality assurance program for German hospitals, which focuses the treatment quality in ovarian cancer (OC). This evaluation gives insight into common treatment patterns and efficacy of guideline-directed therapy of patients with partially platinum-sensitive (PPS) recurrent ovarian cancer (ROC).

Methods The QS OVAR 2004 and 2008 included patients with histologically-proven invasive epithelial OC diagnosed in the third quarter of either 2004 or 2008. These patients were followed over 4 years. PPS was defined as diagnosis of ROC at 6-12 months after primary treatment. For analysis of quality of care and adherence to guidelines, as well as outcome in terms of survival, patients must have had received primary treatment and survived for >28 days after diagnosis of PPS to adjust for non-adherence in patients attending the centre who were already critically ill.

Results A total of 1354 patients in the QS OVAR program received primary treatment and 443 (32.7%) of these had no recurrence until last follow-up. PPS recurrence was diagnosed in 233 (17.2%) patients. The vast majority of PPS patients had stage IIIC (151/64.8%) or IV (50/21.5%) disease at primary diagnosis, and only 35.3% (n=82) had a macroscopic complete resection at primary surgery. Twenty-four (10.3%) patients with PPS survived for <28 days. Of the 209 (89.7%) patients who survived >28 days, 32 (15.3%) received no chemotherapy, 102 (58.3%) received platinum-based chemotherapy (CTX) and 73 (41.7%) received a non-platinum-containing regimen. According to German guidelines, 114 (54.6%) patients received standard treatment consisting of platinum-based combination therapy or pegylated liposomal doxorubicin monotherapy, 63 (30.1%) received a non-standard treatment and 32 (15.3%) received no CTX. There was a significant improvement in median survival after standard treatment (23.3 months) *versus* non-standard treatment (15.3 months) and no CTX (6.2 months, p=0.004).

Conclusions Nearly half of patients with PPS did not receive treatment according to the national guidelines. Adherence to guidelines is a quality indicator with significant impact on prognosis in PPS ROC.

Key words: chemotherapy, ovarian cancer, partially platinum-sensitive recurrence

Introduction

The majority of ovarian cancer patients experience recurrent disease within the first 5 years after primary diagnosis. Therapy of recurrent disease aims to improve quality of life by relieving symptoms but also may improve progression-free and overall survival. Treatment options include cytoreductive surgery in selected patients and systemic treatment with chemotherapy and biological agents. The choice of therapy depends on the type and extent of prior treatments, taking into account toxicity profile, treatment sequences and activity of the last platinum-based primary chemotherapy. The duration of the treatment-free interval (TFI) from last

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platinum course to diagnosis of recurrent disease defines the categorization into platinum refractory (progressive disease under platinum, TFI=0), platinum resistant (TFI <6 months), partially platinum-sensitive (TFI 6-12 months) and platinum-sensitive (TFI >12 months).

This old and arbitrary classification has elements of uncertainty because many clinical factors influence allocation to a particular group. Others factors that impact on TFI include: surgical outcome and stage at primary diagnosis [1]; tumor biology and inherited or acquainted chemoresistance; methods, time intervals and diagnostics tools utilized during follow-up [2]; and maintenance therapy [3, 4].

German treatment guidelines define standard therapeutic options in partially platinum-sensitive (PPS) recurrent ovarian cancer (ROC) primarily as platinum-based combination chemotherapies; however, a non-platinum based combination of pegylated liposomal doxorubicin (PLD) and trabectedin is also recommended in patients for whom a platinum-based combination seems inappropriate.

Randomized phase III studies in platinum-sensitive ROC identified paclitaxel, gemcitabine and PLD as effective combination partners for carboplatin [5-7]. As a result, the German guidelines state that carboplatin combination therapy with the above-mentioned agents is recommended for platinum-sensitive ROC. Furthermore, PLD in combination with trabectedin is recommended as an alternative where there are contraindications for platinum-based chemotherapy [8, 9].

More recently, biological agents such as the anti-VEGF-antibody bevacizumab (in combination with carboplatin/gemcitabine followed by bevacizumab maintenance) and the PARP-inhibitor olaparib (as maintenance after platinum-based reinduction therapy) have been shown to be effective in platinum-sensitive ROC and have been approved by the European Medicines Agency [10, 11].

To date, relatively little is known about how the German guidelines are followed in clinical practice. This study provides details of the German QS OVAR quality assurance program to determine adherence to treatment guidelines in Germany and the effectiveness of guideline-directed therapy for patients with PPS ROC who had been diagnosed with ovarian cancer.

Methods

The QS OVAR quality assurance program was initiated by the German Arbeitsgemeinschaft für Gynäkologische Onkologie (AGO) commission for ovary in 2000, with additional surveys conducted in 2001, 2004, 2008 and 2012. The methods have been described in detail previously [12].

All hospitals with a gynecological unit were contacted via an invitation letter and asked to participate and to provide precise information on the hospital and the patients' primary diagnosis of ovarian cancer in the third quarter of each survey year. When a unit agreed to participate, further detailed information about patient characteristics, histology, surgery and treatment patterns were requested and checked for reliability. Follow-up was performed annually for up to 4 years to capture data on recurrent disease and treatment patterns.

Evaluation of recurrent disease was restricted to patients who had received primary treatment because these were the only patients in whom it was possible to determine platinum-sensitivity. Deaths of unknown cause or unknown disease status were classified as recurrent disease. PPS recurrent ovarian cancer was defined as a treatment-free interval of 6-12 months after primary treatment.

To be included in the analysis of quality of care, treatment guideline adherence and survival, patients had to survive for >28 days after the diagnosis of PPS. This was to adjust for non-adherence in patients with very limited life expectancy and for the feasibility of treatment in seriously ill patients.

The endpoint of this evaluation was "therapy for recurrent disease according to guideline standard" and "survival after recurrence". The survey recorded surgery for recurrent disease and administration of different chemotherapy regimens, which were defined as conforming to guidelines (standard) or not (non-standard). The definition of standard treatment was based on recommendations in the German S2k-guideline that was applicable during the time of the surveys and the years of follow-up. The guideline recommended treatment of PPS ROC with platinum-based combination therapy with paclitaxel or gemcitabine as the primary standard. In addition, the combination of carboplatin with PLD was allowed as a standard based on the results of the CALYPSO study that became available during the survey/follow-up period [7]. Therapy with PLD, with or without trabectedin, was also allowed as a standard treatment in light of the OVA-301 study results that were also applicable during the study period [8, 9].

Statistical analyses were performed with SPSS for Windows Version 15.0 (SPSS Inc., Chicago, IL, USA). All analysis were descriptive in nature. For estimation of survival, the Kaplan-Meier-method was used. The log-rank test was performed to test for differences in time-to-event functions. All p-values are two sided and descriptive; p-values ≤ 0.05 were considered statistically significant. α-adjustment was not performed, so that all p-values are exploratory only.

Results

A total of 245 and 240 hospitals participated in QS OVAR in 2004 and 2008, respectively. This represents 42% and 44%, respectively, of all German hospitals with a gynecological

unit. The total number of patients treated during the third quarter sampling period was 763 in 2004 and 881 in 2008, accounting for up to 45% of all patients diagnosed with epithelial invasive ovarian cancer in Germany during each sampling period.

Six-hundred and eight (79.7%) and 746 (84.7%) patients in the 2004 and 2008 surveys received primary therapy with surgery, chemotherapy, or both. Seventy-two patients (5.3%) had platinum-refractory tumors, 286 (21.1%) had platinum-resistant tumors, 233 (17.2%) had partially platinum-sensitive tumors and tumors were platinum-sensitive in 320 patients (23.6%). There was no evidence of recurrent disease after a median follow-up of 32.9 months in 443 patients (32.75%).

Patient characteristics are shown in Table 1. The PPS group is characterized by a more unfavorable prognostic profile compared with the platinum-sensitive group: more PPS patients had suboptimal surgery, poor general health status and stage IV disease. However, comparison of patient characteristics of the PPS group with the platinum-resistant group underlines the fact that PPS falls into an intermediate prognostic group, with fewer patients who had suboptimal surgery and better general health status.

Fifty-five of 233 (23.6%) PPS patients received no chemotherapy, which was partly part due to the 24 patients (10.3%) who lived for <28 days after diagnosis of PPS (Table 2). Of the remaining 209 patients, 32 (15.3%) who survived for >28 days received no chemotherapy, 102 (58.3%) had platinum-based chemotherapy and 73 (41.7%) were treated with non-platinum chemotherapy. Surgery was performed in 51 of patients (24.4%) with PPS and survival >28 days, including 9 patients (4.3%) who underwent surgery without any chemotherapy.

One hundred and seventy-seven patients (84.7%) with PPS and survival >28 days were treated with chemotherapy (Table 2). Guideline adherence data were available for 90 patients (51.4%) who received platinum-based combination chemotherapy and 24 (13.7%) who were treated with PLD. Overall, 114 patients (54.6%) with PPS ROC and survival >28 days received standard treatment, 63 (30.1%) received non-standard treatment and 32 (15.3%) received no chemotherapy (Figure 1). A detailed description of the different che-

Table 1. Patient characteristics, overall and by platinum-sensitivity category

	Total	Platinum-sensitive (TFI 12+)	Partially platinum-sensitive (TFI 6-12)	Platinum-resistant (TFI 0-6)	Platinum-refractory (pPD)
Patients, n (%)	911 (100)	320 (23.6)	233 (17.2)	286 (21.1)	72 (5.3)
Age, years [median (range)]	66.0 (19-90)	64.6 (32-84)	65.6 (32-85)	67.4 (19-87)	71.4 (30-90)
Comorbidity					
Yes	264 (29.0)	72 (22.5)	59 (25.3)	96 (33.6)	37 (51.4)
No	647 (71.0)	248 (77.5)	174 (74.7)	190 (66.4)	35 (48.6)
Postoperative residual disease, n (%)					
0 cm	336 (37.0)	178 (55.6)	82 (35.3)	63 (22.0)	13 (18.6)
>0 cm	572 (63.0)	142 (44.4)	150 (64.7)	223 (78.0)	57 (81.4)
General health status, n (%)					
Good	293 (32.2)	128 (40.0)	78 (33.5)	75 (26.2)	12 (16.7)
Somewhat limited	382 (41.9)	133 (41.6)	99 (42.5)	128 (44.8)	22 (30.6)
Requires assistance	133 (14.6)	36 (11.3)	34 (14.6)	46 (16.1)	17 (23.6)
Poor	77 (8.5)	10 (3.1)	15 (6.4)	34 (11.9)	18 (25.0)
NA	26 (2.9)	13 (4.1)	7 (3.0)	3 (1.0)	3 (4.2)
FIGO, n (%)					
IA-IIA	52 (5.7)	33 (10.3)	9 (3.9)	11 (3.8)	2 (2.8)
IIB-IIIB	117 (12.8)	56 (17.5)	23 (9.9)	30 (10.5)	8 (11.1)
IIIC	555 (60.9)	190 (59.4)	151 (64.8)	171 (59.8)	43 (59.7)
IV	184 (20.2)	41 (12.8)	50 (21.5)	74 (25.9)	19 (26.4)

FIGO: International Federation of Gynecology and Obstetrics; NA: not available; pPD: progressive disease under platinum; TFI: treatment-free interval.

Table 2. Treatment patterns in partially platinum-sensitive recurrent ovarian cancer

	Survival >28 days after diagnosis of PPS		Survival <28 days after diagnosis of PPS		Total PPS patients	
Patients, n (%)	209 (89.7)		24 (10.3)		233 (100)	
Follow-up, months [median (range)]	32.2 (13.4-55.9)		13.7 (7.1-18.6)		29.9 (7.1-55.9)	
Therapy*						
Any	186	89.0	1	4.2	187	80.3
Surgery	51	24.4	0	0.0	51	21.9
Chemotherapy	177	84.7	1	4.2	178	76.4
Platinum-based	102	58.3	1	100.0	103	58.5
Monotherapy	12	6.9	0	0.0	12	6.8
Combination	90	51.4	1	100.0	91	51.7
Non-platinum	73	41.7	0	0.0	73	41.5
PLD	24	13.7	0	0.0	24	13.6
Topotecan	26	14.9	0	0.0	26	14.8
Gemcitabine	6	3.4	0	0.0	6	3.4
Other	19	9.7	0	0.0	19	9.7
Missing data	2	1.1	0	0.0	2	1.1
No chemotherapy	32	15.3	23	95.8	55	23.6
No surgery and no chemotherapy	23	11.0	23	95.8	46	19.7
Surgery only	9	4.3	0	0.0	9	3.9

* Patients can be in more than one therapy category. PLD: pegylated liposomal doxorubicin; PPS: partially platinum-sensitive.

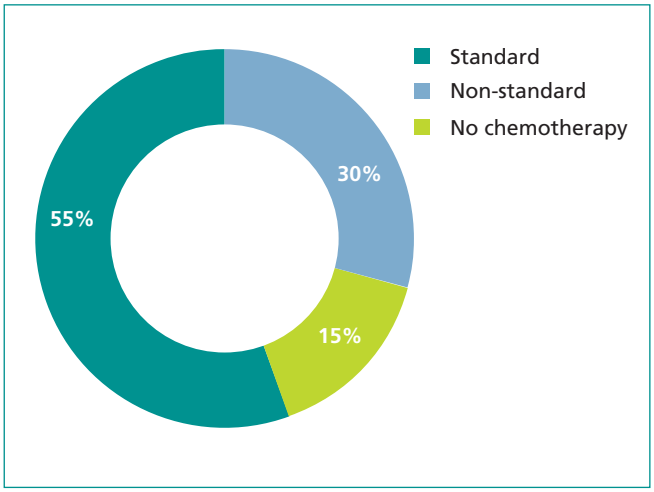

Fig. 1. Guideline-based adherence in patients with partially platinum-sensitive recurrent ovarian cancer and survival >28 days from diagnosis (n=209).

motherapy regimens used in PPS ROC is given in Table 3. Adherence to guideline-directed treatment was associated with a significantly better overall survival. Median overall survival in 114 patients who received standard treatment was 23.3 months *versus* 15.3 months in 63 patients who were treated with a non-standard regimen and 6.2 months in 32 patients who did not receive any chemotherapy (p=0.004) [Figure 2].

Discussion

The aim of the QS OVAR program is to provide transparency on barriers and adherence to guideline standards, as well as to increase awareness about the importance of using guideline-mandated standard treatment options [12, 13].

The first two QS OVAR surveys in 2000 and 2001 were conducted in primary ovarian cancer only, but the surveys in 2004, 2008 and 2012 also included recurrent disease. Although data from the QS OVAR 2012 survey are not yet finalised, the results of the 2004 and 2008 surveys provide definitive data on the treatment of ROC in Germany.

Retrospective evaluation of treatment quality has a number of limitations, including an inability to capture data on patient preference, persisting toxicities and relevant comorbidities, as well therapeutic limitations due to frailty or other factors. We tried to address some of these issues by including only patients who received primary treatment and survived or ≥28 days after the diagnosis of ROC. The validity of this approach was highlighted by results showing that only one

Table 3. Details of the different chemotherapy regimens used in partially platinum-sensitive recurrent ovarian cancer

Chemotherapy regimen	Recipients [n=177, n (%)]
Platinum-based	103 (57.9)
Platinum monotherapy	12 (6.7)
Platinum/taxane	48 (27.0)
Carboplatin/paclitaxel	44 (24.9)
Carboplatin/docetaxel	2 (1.1)
Cisplatin/paclitaxel	1 (0.6)
Platinum/antimetabolite	28 (15.7)
Carboplatin/gemcitabine	26 (14.6)
Platinum/capecitabine	2 (1.1)
Platinum/anthracycline (carbo/PLD)	12 (6.7)
Platinum/alkylating agent	1 (0.6)
Platinum/topo-inhibitor (carbo/topo)	2 (1.1)
Non-platinum regimens	73 (41.0)
Anthracyclines (24 x PLD, 1 x mitoxantrone)	25 (14.0)
Taxane (5 x paclitaxel, 1 x docetaxel)	6 (3.4)
Alkylating agents (treosulfan)	4 (2.2)
Antimetabolites (6 x gemcitabine, 1 x pemetrexed)	7 (3.9)
Topo-inhibitor (topotecan)	24 (13.6)
Taxane + topo-inhibitor (docetaxel/etoposide)	1 (0.6)
Antimetabolite + alkylating agent (capecitabine/treo)	1 (0.6)
Antimetabolite + anthracycline (gemcitabine/PLD)	1 (0.6)
Antimetabolite + others	1 (0.6)
Anthracycline + others	1 (0.6)
Missing data	2 (1.1)

* Carbo: carboplatin; PLD: pegylated liposomal doxorubicin; Topo: topoisomerase; Treo: treosulfan.

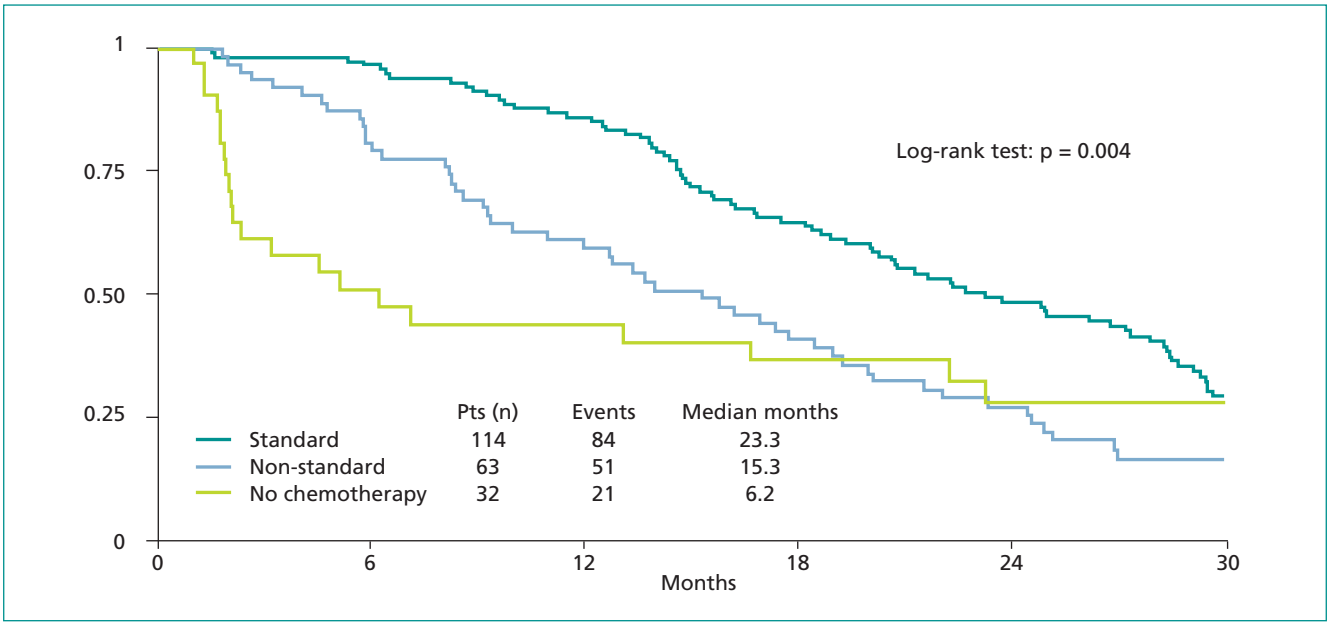

Fig. 2. Overall survival in patients with partially platinum-sensitive recurrent ovarian cancer who survived >28 days after diagnosis of recurrent disease (n=209).

of the 24 patients who died within 28 days after diagnosis of PPS actually received chemotherapy.

The patient characteristics recorded confirmed that PPS is a patient group characterized by intermediate prognostic risk, between highly platinum-sensitive (>12 months TFI) and platinum-resistant (<6 months TFI) ROC. This intermediate position may result in a more heterogeneous choice of treatment, but this is not enough to explain all the observations made in our study. Nearly half of all patients with PPS did not receive the recommended standard treatment. It is important to note that our definition of standard treatment was quite broad because, at the time the first survey was conducted, standard treatments including carboplatin + PLD, PLD ± trabectedin and other non-evidence-based platinum combination chemotherapy regimens were defined as standard but were not yet available. Surgery was performed in nearly a quarter of PPS patients (24.4%) despite that fact that the impact of surgery in recurrent disease is not clear, although there is indirect evidence from retrospective studies that selected patients might benefit from macroscopic complete resection [14, 15]. An ongoing prospective study (AGO-OVAR OP.4 DESKTOP III; NCT01166737) is close to completing recruitment and will hopefully provide data on whether surgery should be recommended as a standard approach in selected patients with platinum-sensitive recurrence (the study includes all patients with a TFI >6 months).

The study results showed that 15.3% of patients with PPS ROC who survived for >28 days did not receive any chemotherapeutic treatment. Given that the median survival time in these patients was 6.2 months, it seems difficult to justify the withholding of potentially effective and tolerable therapies. However, the QS OVAR data cannot provide explanations for these observations. This is also the case for the use of non-standard chemotherapy regimens in 30% of PPS ROC patients. What is even more concerning is that these non-evidenced chemotherapies were partly used as toxic combination therapies, which contradicts all the therapeutic aims in ROC, which is the delicate balance between efficacy, tolerability and quality of life. Guideline-based recommendations for PPS treatment provide multiple chemotherapeutic options, including a non-platinum alternative, and allows the selection of an appropriate and individualized therapy. Treatment with non-standard regimens should therefore be restricted only to a few specific cases.

Survival analysis showed that guideline-based treatment was associated significantly better overall survival (median 23.3 months *versus* 15.3 months in those treated with non-standard therapy and 6.2 months in patients who did not receive chemotherapy). The implication of these results is that not using standard treatment in PPS ROC patients decreases their life span by 8 months, and nearly 1.5 years of life could be lost if no chemotherapy is given.

The lack of adherence to evidence-based treatment guidelines and the heterogeneity of chemotherapy regimens used in this survey suggests that physicians lack confidence or are not aware of established standards. The goals of programs such as QS OVAR in Germany are to highlight knowledge deficits and to increase awareness of effective and evidence-based treatment options. Over the time of the QS OVAR surveys there has been improvements in the first-line treatment options available for PPS ROC, and promising results for some second-line therapies. In addition, physicians need to be familiar with the a comprehensive guideline on diagnostics, therapy and follow-up of malignant ovarian tumors, published by the AGO commission for ovary, which provides updated and specific recommendations for the treatment of ovarian cancer [16].

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