Arch Gynecol Obstet (2009) 280:719–724
DOI 10.1007/s00404-009-0995-2

ORIGINAL ARTICLE

Systemic therapy developments and their effects regarding the current concept of recurrent ovarian carcinoma as a chronic disease

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Received: 22 December 2008 / Accepted: 5 February 2009 / Published online: 22 February 2009

Abstract
Purpose To demonstrate how the current concept of recurrent ovarian carcinoma (ROC) as a chronic disease resulted in developments in the systemic treatment strategies and outcome over time.
Methods We compared therapy type and course of a population-based cohort whose recurrent disease was diagnosed from 1990 to 2006. We divided the patients into two subgroups depending on the year of diagnosis of ROC (group A 1990–1997, $n = 70$; group B 1998–2006, $n = 63$).
Results Both study groups showed similar results in survival (median recurrent disease-specific survival—A 18 months vs. B 19 months; $P = 0.549$). In group B, the patients had significantly fewer combination therapies administered [12.0% vs. 24.1%; odds ratio (OR) 0.43; 95% confidence interval (CI) 0.23–0.81; $P = 0.0057$], received more therapy lines (≥3 lines 56.1% vs. 31.1%; OR 3.10; 95% CI 1.37–7.17; $P = 0.005$) and had significantly longer times of treatment (TT) in relation to the survival time (ST; mean TT/ST-ratio 57.5% vs. 47.5%; difference of the mean values B–A = −10.02; 95%CI −17.99 to −2.05; $P = 0.014$).
Conclusions The finding that survival of ROC patients could not be improved over time should not necessarily be viewed with undue pessimism regarding the general therapy situation. In the more recent study period, a similar outcome could be achieved with less aggressive treatment regimens, i.e., with fewer combination therapies and with longer treatment periods using less toxic agents. When a disease which requires periodic chemotherapy to control progressive course is increasingly treated with a strategy that permits stabilization with limited cumulative toxicity, then the requirements of a chronic disease management have been fulfilled.

Keywords Ovarian carcinoma · Recurrent disease · Chronic disease · Chemotherapy · Outcome

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Introduction

In the last decade, recurrent ovarian carcinoma (ROC) has become increasingly viewed as a chronic disease process [1–3]. There exists a vast amount of literature concerning the systemic therapy of ROC (overview in: [1, 3–8]), but there are no reports that focus on how this current concept has actually altered the clinical management of the disease. Nearly all clinical trials concentrate only on the feasibility and impact of defined therapy options, usually in second-line treatment situations early after the initial diagnosis of ROC. They focus on the evaluation and comparison of particular antineoplastic agents and drugs, but in doing so, can only evaluate particular therapy options in pre-selected groups of patients in certain situations. Thus, their ability to describe the overall course of recurrent disease is limited.

The goal of this study was to depict a clear and cohesive picture of the palliative treatment setting over a 17-year period in an unbiased study cohort and to analyze changes and developments in treatment strategies and patient outcome. By doing so, we could evaluate how the current

concept of ROC as a chronic disease affected the choice of systemic therapies.

Patients and methods

The Basel Ovarian Carcinoma Data Base is comprised of extensive data concerning clinical, histo- and pathomorphologic features and treatment characteristics of all patients whose primary epithelial ovarian cancer was diagnosed in the canton Basel-Stadt (Basel, Switzerland) since 1985. For this study, we considered the data from patients who were initially diagnosed with ROC from 1990 to 2006. Most of the patients had International Federation of Gynecology and Obstetrics (FIGO) stages I–III at initial diagnosis ($n = 121$). In the remaining 12 patients who were classified as having stage IV disease, the grouping into this stage was based only on the diagnosis of pleural involvement and/or liver parenchymal metastases; patients with other distant metastases (lesions beyond the abdominal cavity) were excluded from analysis. Since the use of palliative chemotherapy options was the crucial factor evaluated in this study, we did not include patients for whom the choice of possible treatment options were limited by advanced age (older than 75 years).

Ultimately, 133 patients were analyzed in this study. No patient was lost to follow-up and we could provide complete information regarding palliative therapy course and outcome for all patients. Information concerning palliative treatment was obtained from 12 oncologic units in Switzerland, as well as neighboring regions in Germany and France. The patients were followed until death or, if they remained alive and disease-free, for a minimum of 24 months (conclusion of the data collection in July 2008).

It was the goal of our study to give a general overview regarding the actual administered therapies in the systemic treatment of ROC and to demonstrate changes and developments over time. Therefore, we compared the therapy course and outcome of women whose recurrent disease was diagnosed up to and including 1997 (group A $n = 70$) with those whose recurrent disease was diagnosed after 1997 (group B $n = 63$). We listed the number of therapy lines and noted the agents administered. Furthermore, the duration of each therapy line, and importantly the cumulative time of treatment, was recorded for each patient. In our study, survival was defined as the interval from the date of diagnosis of ROC to the date of death. In this manner, the recurrent disease-specific survival (RDSS) was calculated.

To evaluate the role of the duration of systemic treatment on survival time in ROC, we calculated the ratio between cumulative time of therapy (TT) and survival time (ST), and expressed this as a percentage:

$$\frac{\mathrm{TT} \times 100}{\mathrm{ST}}$$

For example, a patient who survived 16 months (64 weeks) and received chemotherapy for a total of 24 weeks would have a treatment time to survival time (TT/ST) ratio of 37.5. This means that systemic treatment had been administered for 37.5% of the patient's survival time.

For this particular purpose, we analyzed only the patients who ultimately died of their recurrent disease. In other words, we analyzed only completed treatment courses and excluded patients who were still alive at the conclusion of the observation period (i.e., whose therapies were presumably still ongoing).

The study design and data collection methods were approved by our institutional review board.

Statistical analysis

To predict the survival with ROC (RDSS), we used the Kaplan–Meier method. Patients who were alive at the conclusion of the observation period were censored in the statistical analyses. Statistical differences between groups in terms of survival curves were analyzed using the log rank test. To compare ordinal variables (number of therapy lines) between the two study groups, the nonparametric Wilcoxon test was performed. The calculation of the TT/ST-ratio was made by the Welch two sample *t*-test. Comparisons between nominal parameters were made with the Fisher exact test. A P value <0.05 was considered significant. For significant values, the odds ratio (OR) and the corresponding 95% confidence interval (CI) were reported. Statistical analyses were performed with R Development Core Team software, version 2.7.0 (Vienna, Austria).

Results

The clinicopathologic and outcome characteristics of the 133 patients with ROC included in the study are summarized in Tables 1 and 2. The majority of the patients with ROC included in this study died of the disease (group A $n = 70$, 100%; group B: $n = 57$, 90.5%). Six patients in group B were alive at the conclusion of the observation period; four of them have ongoing palliative therapies. In two further patients, localized recurrent disease was diagnosed. In one case, a 47-year old woman had a recurrent tumor mass in the pelvis, which was surgically removed (no postoperative residual disease), and postoperatively received a second-line chemotherapy with six cycles of carboplatin and paclitaxel. The other patient had a histologically proven recurrence as a fixed pelvic mass eroding the vaginal mucosa. This 74-year old patient was treated

Table 1 Clinicopathologic and outcome characteristics of 133 patients with recurrent ovarian carcinoma

Variable	Group A	Group B
Entire group, *n* (%)	70 (100)	63 (100)
FIGO stage at initial diagnosis		
Stage I	5 (7.1)	3 (4.8)
Stage II	14 (20.0)	5 (8.0)
Stage III	44 (62.9)	50 (79.3)
Stage IV	7 (10.0)	5 (7.9)
Histologic subtype		
Serous	48 (68.6)	49 (77.8)
Mucinous	4 (5.7)	2 (3.2)
Endometriod	15 (21.4)	8 (12.7)
Clear-cell	3 (4.3)	4 (6.3)
Postoperative chemotherapy (CT)		
Platinum-based CT	64 (91.5)	61 (96.8)
CT without platinum compounds	5 (7.1)	–
No CT	1 (1.4)	2 (3.2)
Relapse free period		
<6 months	29 (41.4)	23 (36.5)
≥6 months	41 (58.6)	40 (63.5)
Age at diagnosis of recurrent disease		
Mean (range)	58.6 years (36–75)	58.2 years (29–75)
≤59 years	34 (48.6)	32 (50.8)
60–75	36 (51.4)	31 (49.2)
Outcome status		
Died of ovarian cancer	70 (100)	57 (90.5)
Died of other causes	–	–
Alive (ongoing therapy with evident disease)	–	4 (6.3)
Alive (no evidence of disease >48 months)	–	2 (3.2)

Group A recurrent disease first diagnosed 1990–1997, $n = 70$

Group B recurrent disease first diagnosed 1998–2006, $n = 63$

CT chemotherapy, *FIGO* International Federation of Gynecology and Obstetrics

with six cycles of carboplatin as monotherapy. These two patients have experienced a long asymptomatic period (49 and 55 months) up until the conclusion of the observation period; one might even consider them as potentially cured. Two patients in study group A had isolated brain metastases, i.e., no recurrent disease in the abdominal region. These patients received only radiotherapy. All other patients included in the study had recurrence in abdominal sites as a manifestation of recurrent disease.

A comparison between both groups in terms of RDSS showed similar findings (Fig. 1; $P = 0.549$). The 1-year adjusted survival rate was 65.7% for patients whose ROC was diagnosed before 1998 (group A) compared to 69.8% in those whose ROC was diagnosed later (group B); the

Table 2 Survival time after diagnosis of recurrent disease of the patients who died of ovarian carcinoma

	Group A	Group B
<6 months	11 (15.7)	7 (12.3)
6–12 months	13 (18.6)	12 (21.1)
13–24 months	22 (31.4)	18 (31.6)
25–48 months	15 (21.4)	17 (29.8)
>48 months	9 (12.9)	3 (5.3)
Median survival time (range)	18 months (1–129)	19 months (1–102)

Group A recurrent disease first diagnosed 1990–1997, $n = 70$

Group B recurrent disease first diagnosed 1998–2006, $n = 57$

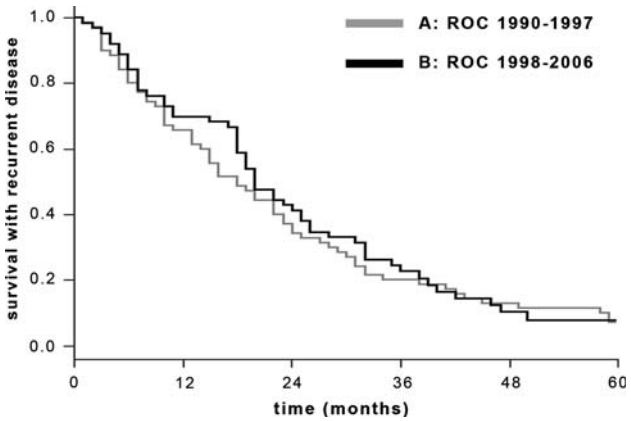

Fig. 1 Recurrent disease-specific survival among 133 patients with recurrent ovarian carcinoma. Group A recurrent disease first diagnosed 1990–1997, $n = 70$; group B recurrent disease first diagnosed 1998–2006, $n = 63$

3-year rates were 20.0 and 22.6%, and the 5-year rates were 7.1 and 7.7%, respectively. The median RDSS time was 18 months in group A and 19 months in group B.

Tables 3 and 4 indicate which systemic therapies the patients in each group received, as well as the number of lines administered. In group B, representing the current therapy situation, significantly fewer combination therapies were administered compared to group A (12.0% vs. 24.1%; OR 0.43; 95% CI 0.23–0.81; $P = 0.0057$). The patients in group B received slightly more therapy lines, but this did not reach statistical significance (median number of lines 3 vs. 2, mean 2.73 vs. 2.35; $P = 0.139$). In group B, there were significantly more patients who received at least three therapy lines (56.1% vs. 31.1%; OR 3.10; 95% CI 1.37–7.17; $P = 0.005$).

Analysis of the TT/ST-ratio showed that the patients in group B had significantly longer TT in relation to the survival time (mean value in group A 47.5, mean value in group B 57.5; difference of the mean values B–A = −10.02; 95% CI −17.99 to −2.05; $P = 0.014$).

Table 3 Number of therapy lines received by patients who died of recurrent ovarian carcinoma

	Group A	Group B
Total no. of patients, *n* (%)	70 (100)	57 (100)
No systemic therapy	6 (8.6)	5 (8.8)
One therapy line	17 (24.3)	11 (19.3)
Two therapy lines	25 (35.7)	9 (15.8)
Three therapy lines	7 (10.0)	14 (24.6)
Four therapy lines	10 (14.3)	9 (15.8)
Five therapy lines	1 (1.4)	6 (10.5)
Six therapy lines	3 (4.3)	2 (3.5)
Seven therapy lines	–	1 (1.7)
Nine therapy lines	1 (1.4)	–

Group A: recurrent disease first diagnosed 1990–1997, $n = 70$

Group B: recurrent disease first diagnosed 1998–2006, $n = 57$

Table 4 Agents administered for the treatment of recurrent ovarian carcinoma. List includes also patients with ongoing therapies

	Group A	Group B
Agent, %		
Carboplatin	34.7	31.0
Liposomal doxorubicin	2.0	19.7
Paclitaxel	14.6	10.7
Gemcitabine	3.0	19.2
Topotecan	2.5	9.1
Melphalan	14.6	–
Cyclophosphamid	10.1	1.1
Cisplatin	4.0	1.1
5-Fluoruracil	2.5	–
Capecitabine	1.0	1.1
Docetaxel	1.0	–
Folinic acid	1.5	–
Etoposid	1.5	1.1
Vinorelbine	–	1.6
Aflibercept (VEGF trap)	–	1.1
Adriblastin	–	1.1
Treosulfan	–	1.6
Others	2.0	–
Intraperitoneal chemotherapy		
Carboplatin	1.5	0.5
Cisplatin	2.0	–
5-Fluoruracil	2.0	–
Others	1.0	–

Group A recurrent disease first diagnosed 1990–1997, $n = 70$

Group B recurrent disease first diagnosed 1998–2006, $n = 63$

Discussion

The leading chronic diseases in developed countries include disorders such as cardiovascular diseases (e.g., high blood pressure, stroke), diabetes, obesity, arthritis, respiratory ailments (e.g., emphysema and bronchial asthma) and neurologic diseases (e.g., epilepsy and multiple sclerosis). Chronic diseases are by definition long-lasting or recurrent, i.e., require a long period of treatment, supervision, observation or care; they are caused by non-reversible pathological alterations, leave residual disability, and can be altered but not be cured by medication [9, 10]. A therapeutic goal in the management of chronic diseases is long-term stabilization with good tolerance to drugs that have limited cumulative toxicity.

Although in principle, most metastatic malignancies can also be considered as chronic diseases due to their incurable nature, the term "chronic disease" is usually not used for most malignant diseases in oncologic reviews; it is, however, specifically mentioned in the current literature concerning ROC [1–3]. However, it is not discussed in more detail how this current concept affects specifically the clinical management of ROC patients. Clinical trials concerning the systemic therapy of ROC usually have not considered the concept of it as a chronic disease process (overview in [1, 3–8]). They evaluated mostly therapy options in the second-line treatment setting, in other words, only at the beginning of the ROC period. Only a few trials have evaluated the clinical efficacy of third-, fourth- or fifth-line therapies [11].

Our study aimed to highlight the current developments in the management of ROC, which justify its consideration as a chronic disease and focused on the changes in systemic therapy of ROC over time. In order to evaluate the treatment course of a chronic disease, it is essential to give an overview of the entire course of the disease. This was achieved in our study through the analysis of a population-based study cohort. Since there has been considerable change in the last two decades in the number and type of agents available, we divided the patients of our study group into two subgroups according to the date of initial diagnosis of recurrent disease.

The first main result of our study showed that survival times of patients with ROC had not improved over the entire study period. However, this initially disappointing finding should not necessarily be viewed with undue pessimism regarding the therapy of ROC. Particularly, one should not interpret this as meaning that there have been no improvements or progress in the treatment of patients with ROC. The primary goal of palliative treatment includes not only prolongation of survival, but, just as importantly, the prevention and relief of symptoms, and maintenance or improvement of quality of life. Our analysis of the administered agents showed that, in the more recent study period (study group B treatment since 1998), a similar

survival time with significantly fewer combination therapies and with longer treatment periods (i.e., higher TT/ST values) could be achieved. Both of these findings suggest that the administration of less aggressive treatment regimens resulted in similar outcomes. Clearly, the avoidance of combination therapies and the increased use of monotherapies reduce treatment-related toxicities; furthermore, longer treatment periods and the administration of more therapy lines (in study group B, 56% of the patients received more than two therapy lines) are possible only when the quality of life has not been intolerably affected. In accordance with other authors, we believe that choosing agents with few or tolerable toxicities that can be given on a convenient schedule over a prolonged period of time is an acceptable way to manage ROC [3]; however, controversy exists regarding an appropriate time to stop such therapy.

Since improvements in palliative therapy do not only imply extended survival but also improved overall quality of life, current treatment strategies may very well reflect improvements in the systemic palliative treatment of patients with ROC. Furthermore, when a disease which requires periodic chemotherapy to control progressive course and symptoms is increasingly treated with a strategy that permits stabilization and uses regimens that have limited cumulative toxicity, then the requirements of a chronic disease management have been fulfilled [1].

We think that the paradigm shift in the palliative treatment of ROC as chronic disease cannot be attributed to a certain date or the introduction of a single agent or regimen. In clinical reality, there is often a slow shift or interplay between theory and the therapy options that might result in a significant change in the general regard of a disease. Improvements in the systemic treatment of ROC are surely associated with the introduction of a new generation of cytotoxic agents, above all, liposomal doxorubicin, gemcitabine and topotecan. As demonstrated in Table 4, while platinum and paclitaxel remained viable options in the systemic treatment of ROC, these modern agents made up approximately 48% of therapies in patients whose ROC was diagnosed after 1997, while in the preceding period only 7%. Certain drugs which were used in the earlier study group (e.g., melphalan, cyclophosphamid and cisplatin) have mostly been replaced. Undoubtedly, through the selection of modern drugs with safer profiles, and of course through considerable advances in supportive care, the therapy concepts of chronic disease can be better implemented today compared to earlier times.

One limitation of our study must be considered: we did not distinguish between the prognostically relevant subgroups of platinum-resistant and platinum-sensitive patients. These specific definitions are essential for clinical trials to ensure uniformity of design and patient selection. From a clinical perspective, however, these definitions may be arbitrary [1]. The principle of second-line therapy is that if the treatment is successful, patients will eventually have another recurrence and undergo additional rounds of therapy. In this sense, platinum-sensitive and resistant disease are not necessarily different entities in terms of the concept of a chronic disease.

In the palliative setting, there is currently no agreed upon approach for the treatment of this heterogeneous group of ROC patients [12]. With respect to ROC as a chronic disease, it is interesting to observe the controversies surrounding the optimal second-line treatment of platinum-sensitive patients. The question is whether these patients should be offered a single-agent treatment (platinum alone) or a combination therapy (platinum plus another agent, e.g., paclitaxel [13], gemcitabine [14] or liposomal doxorubicin [15]. Some authors support the administration of combination therapies, since they result in improved response rates and progression-free survival compared with single-agent platinum [1, 4]. Others are more critical concerning the use of combination therapies and feel that the improvement in response is at the cost of toxicity and quality of life [2, 3, 5, 6, 16]. Furthermore, combination therapies may not have much of a clinically apparent advantage compared with sequential single-agent therapy with regard to overall survival, and it may be possible to achieve the same efficacy by sequencing platinum and other agents without the increase in toxicities observed with combination therapy [3, 5, 6]. Particularly, with respect to the increasing use of subsequent therapy lines, it must be emphasized that patients with a history of severe side effects associated with previous treatment might be poorer candidates for further treatments [1].

Considering ROC in the context of chronic disease, it must be pointed out that clinical trials evaluating combination therapies vs. monotherapy report overall survival rates, but they do not report the number of subsequent therapy lines and the choice of agents given after the trial up until death [13–15]. The use of multiple therapies after the completion of a randomized study in ROC might obscure the benefit of combination therapy [16]. Since these studies encompass only a fraction of the chronic disease process, their results cannot be completely applied toward the entire course of disease and therapy. In our opinion, the increased application of monotherapies reflects better the concept of ROC as a chronic disease. We prefer administering combination therapies only for highly symptomatic patients. In these cases, the high response rates of the regimen result in rapid alleviation of severe disease-related symptoms and justifies the acceptance of increased toxicity.

In conclusion, we believe that is the first study to depict a population-based image of the palliative treatment situation in ROC and demonstrates how far the concept of ROC as a chronic disease has been implemented in clinical practice. We support the hope that through the availability

and use of newer and more effective systemic agents, including both traditional cytotoxic regimens and new promising targeted biologic agents, the treatment of these patients can be further improved. Future studies should examine not only individual agents or differences between single-agent and combination therapies, but also specific treatment strategies with more than one therapy line over a longer course of time with respect to the concept of ROC as a chronic disease.

Conflict of interest statement The authors declare that they have no conflict of interest.

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