The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy

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Background: Despite recent progress in the treatment of ovarian cancer, the majority of patients eventually relapse. There is little information on the effectiveness of chemotherapy in higher treatment lines.

Patients and methods: Characterization of the second to sixth line therapy and its effects on survival was carried out, based on data of n = 1620 patients from three large randomized phase III trials investigating primary therapy.

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Results: Median progression-free survival (PFS) after the first, second, third, fourth and fifth relapse was 10.2 [95% confidence interval (CI) 9.6–10.7], 6.4 (5.9–7.0), 5.6 (4.8–6.2), 4.4 (3.7–4.9) and 4.1 (3.0–5.1) months, respectively. Median overall survival (OS) after the first, second, third, fourth and fifth relapse was 17.6 [95% CI 16.4–18.6], 11.3 (10.4–12.9), 8.9 (7.8–9.9), 6.2 (5.1–7.7) and 5.0 (3.8–10.4) months, respectively. The most frequent second and third line chemotherapy was platinum combination (n = 313, 24.5%) and topotecan (n = 118, 23.6%), respectively. Relapse treatment improved PFS and OS at the second to fourth recurrence, although frequently not performed according to the standard of care. In multivariate analysis, platinum sensitivity and optimal primary tumor debulking were revealed as independent prognostic factors for PFS up to third relapse.

Conclusion: A maximum of three lines of subsequent relapse treatment seems to be beneficial for patients with recurrent ovarian cancer. Optimal primary tumor debulking and platinum sensitivity remain independent prognostic factors even after more frequent relapses.

Key words: recurrent ovarian cancer, relapse treatment, subsequent relapse, survival

Introduction

Epithelial ovarian cancer is the gynecological tumor with the highest mortality [1] while being the sixth most common cancer in women [2]. Most patients present at an advanced stage of the disease and with limited prognosis [3]. Despite a meaningful improvement in primary therapy (surgery and chemotherapy) during the last decade, a rapid development of resistance to treatment and recurrence is still frequent. About 80% of the patients with advanced stage [Fédération Internationale de Gynécologie et d’Obstétrique (FIGO) II–IV] epithelial ovarian cancer will relapse during or after adjuvant taxane/platinum-based chemotherapy [4]. Therefore, subsequent chemotherapies are often required. In contrast to the first-line therapy, recurrence treatment is less standardized. Nevertheless, at first relapse, treatment can still be highly effective. Especially in the subgroup of patients with platinum-sensitive disease (i.e. recurrence after >6 months after primary platinum-based chemotherapy), a second-line treatment in terms of platinum-based reinduction is able to achieve an improvement of progression-free survival (PFS) and overall survival (OS) [5–7]. Even in the group of patients with platinum-resistant disease (i.e. recurrence within 6 months), a monotherapy can improve PFS [8], although the accepted goal of therapy is to maintain quality of life [9]. Second-line therapies have been increasingly evaluated in randomized phase III trials so that an accepted standard of care could be defined. These treatments comprise several chemotherapeutic regimens that have proven efficacy and that differ in toxicity profiles. Despite this progress in treatment of primary recurrent disease, there is little information as to the outcomes in the second or the subsequent instances of relapse [10]. Therefore, we carried out this exploratory analysis in a prospectively collected database from randomized first-line trials.

Materials and methods

This exploratory analysis was carried out using data from patients originating from three prospectively randomized phase III trials in advanced epithelial ovarian cancer coordinated and carried out by two multicenter study groups, i.e. Arbeitsgemeinschaft Gynäkologische Onkologie Studiengruppe Ovarialkarzinom and Group d’Investigateurs Nationaux pour l’Étude des Cancers Ovariens between 1995 and 2002. All the trials were fully published and details were reported elsewhere [11–13]. The inclusion criteria were comparable in all the three trials: 18+ year-old patients after given written informed consent were enrolled if they had previously untreated epithelial ovarian cancer FIGO stage IIB-IV. The patients were randomly assigned to one of two treatment arms: carboplatin–paclitaxel (TC) versus cisplatin–paclitaxel, TC versus carboplatin–epirubicin–paclitaxel (TEC), and TC versus TC followed by topotecan. Study treatment was assigned by central randomization stratified by center and stratum. Stratum 1 contained patients with FIGO stage IB-III and postoperative residual tumor size of 0–1 cm, stratum 2 contained patients with either FIGO stage IV disease or residual tumor size larger than 1 cm. No significant differences between the compared treatment arms have been shown regarding relapse-free or OS in any of the trials.

Follow-up visits were scheduled every 3 months in the first 2 years after the cessation of treatment and every 6 months thereafter, for a total follow-up time of at least 5 years. The following data of the follow-up form were used in the analysis: (i) the date of progression or death from any cause, the occurrence of a secondary malignancy or Cancer Antigen 125 rise without any clinical sign of relapse was not considered as disease progression, but commonly induced radiological investigations (CT scans); (ii) the date and kind of anticancer therapy and the agents used, if applicable; (iii) the date of death and the cause of death were documented as soon as the investigator became aware of it. Whether and how a patient should be treated in case of relapse was up to the investigator’s discretion.

The documented therapies were independently assigned to the following groups by two of the investigators, i.e. SL and LH: monochemotherapy, chemotherapy combination (i.e. combination of two agents given either simultaneously or subsequently at the same relapse), chemotherapy other (e.g. combinations of more than two agents), hormonal therapy, hyperthermia, immunotherapy, surgery-based therapy, targeted therapy, radiotherapy and other. The patients who underwent surgery for recurrence were assigned to the surgery-based therapy group regardless of receiving additional treatment modalities, e.g. chemotherapy or other, at the same relapse. For analyzing systemic therapies more in detail, chemotherapies, given alone or combined with other treatments, were grouped according to the agents documented: platinum single agent chemotherapy, platinum combination, pegylated liposomal doxorubicin (PLD), topotecan, gemcitabine, taxane, treosulfan, cyclophosphamide, etoposide and other agent in that order. Therapies were considered to be related to progressions if they started within 10 weeks from the progression date. The exploratory analysis was carried out based on 1620 patients. About 1753 patients were excluded from the original dataset of 3373 patients because of the missing data concerning progression and/or therapy, and/or because the dates of therapy and progression could not be related reliably.

OS was calculated from the day of randomization in the source trial and, thereafter, from each subsequent documented disease progression to death.
PFS was calculated from the day of randomization to the first disease progression and, thereafter, from one progression to the subsequent one or to death. Kaplan–Meier estimates and Cox proportional hazards models were used to investigate the impact of different covariates on OS and PFS. All statistical analyses are explorative in nature, and P-values were interpreted descriptively. SAS statistical software (version 9.1.3, SAS Institute, Cary, NC) was used to analyze the data.

**results**

A total of 3388 patients with advanced epithelial ovarian cancer had been included in the three original randomized phase III trials. The median PFS and OS for the whole group were 18.2 [95% confidence interval (CI) 17.3–19.1] and 44.1 (95% CI 42.3–46.4) months, respectively. The corresponding 5-year PFS and OS rates were 22.6% and 39.0%, respectively. In this group, 2393 patients have relapsed and a total of 1973 patients died in the observation period until 2007.

In 2074 patients, at least one relapse treatment was reported after the first-line therapy. Information on subsequent therapies after the first recurrence was evaluable in 1620 patients, i.e. 78.1% of all treated patients. These women were included in the present analysis. The patients’ characteristics are given in Table 1. A total of 4341 treatments were documented. These treatments comprised different treatment modalities such as chemotherapy, hormonal therapy, surgery-based therapy, radiotherapy and others (supplementary Table S1, available at Annals of Oncology online). A total of 3335 chemotherapeutic regimens were administered in 1620 patients, predominantly given as single agent therapy (58.1%) and only in 17.6% as combination therapy. The most commonly used chemotherapeutic regimen for the second-line therapy was a platinum-based combination (n = 313, 24.5%) followed by treosulfan (n = 291, 22.8%) and topotecan (n = 278, 21.8%). Topotecan was the most frequently used agent as third-line treatment (n = 118, 23.6%). The chemotherapeutic agents used at each relapse are shown in supplementary Table S2, available at Annals of Oncology online. After first recurrence, the distribution of polychemotherapy versus monochemotherapy in patients with platinum-resistant and -sensitive disease was 8% versus 57% and 23% versus 44%, respectively (supplementary Table S3, available at Annals of Oncology online).

The most frequently given polychemotherapeutic regimen after the first recurrence was platinum containing regardless of the treatment-free interval. The predominant monochemotherapy in platinum-resistant and -sensitive disease was treosulfan and platinum, respectively (Figure 1A and B). The median PFS and OS in the entire group of patients depending on relapse are shown in Figure 2A and B. Median PFS after the first, second, third, fourth and fifth relapse was 10.2 (95% CI 9.6–10.7), 6.4 (5.9–7.0), 5.6 (4.8–6.2), 4.4 (3.7–4.9) and 4.1 (3.0–5.1) months, respectively. Median OS after the first, second, third, fourth and fifth relapse was 17.6 (95% CI 16.4–18.6), 11.3 (10.4–12.9), 8.9 (7.8–9.9), 6.2 (5.1–7.7) and 5.0 (3.8–10.4) months, respectively. Univariate Cox regression shows the impact of standard prognostic markers of primary diagnosis at each relapse (supplementary Table S4, available at Annals of Oncology online). A stratified Kaplan–Meier analysis according to postoperative tumor residuals reveals a significant longer PFS and OS for patients without any tumor residual after primary surgery up to third recurrence (supplementary Figure S1, available at Annals of Oncology online). At the first, second and third relapse, the PFS of patients with postoperative tumor residuals = 0 cm at the time of the primary surgery compared with tumor residuals >0 cm was 12.1 versus 9.6 months (P < 0.0001), 8.1 versus 5.8 months (P < 0.0001) and 6.8 versus 5.6 months (P = 0.14), respectively. OS at the first, second and third relapse was 22.7 versus 15.9 months (P < 0.0001), 17.6 versus 10.3 months (P < 0.0001) and 10.6 versus 8.4 months (P = 0.31), respectively. The administration of relapse treatment eventuated in an improvement of OS and PFS at the second to fourth recurrence (Figure 3A and B). At the second, third and fourth relapse, the patients undergoing treatment versus no treatment had a PFS of 7.2 versus 3.7 months (P < 0.0001), 6.5 versus 3.0 months (P < 0.0001) and 4.7 versus 3.1 months (P = 0.41), respectively. OS at the second, third and fourth relapse was 14.2 versus 4.1 (P < 0.0001), 10.6 versus 3.3 (P < 0.0001) and 7.7 versus 3.4 (P = 0.0002), respectively. In a multivariate Cox regression analysis, ...
model, Eastern Cooperative Oncology Group performance status (ECOG), FIGO-stage and grading proved their significant impact on PFS up to third relapse (Table 2 A + B). Platinum sensitivity, primary postoperative tumor residuals and relapse treatment tumor residuals were the strongest independent factors for PFS up to the third and fourth recurrence, respectively. The strongest independent prognostic factors for OS were FIGO stage and relapse treatment remaining independent up to the fourth and fifth recurrence, respectively. However, most classical prognostic factors failed at higher recurrences (Table 2 and supplementary Table S4, available at Annals of Oncology online).

discussion

Patients with advanced epithelial ovarian cancer frequently develop resistance to chemotherapy and therefore experience subsequent relapses [14]. Despite increasing evidence in the second-line therapy resulting from several recent phase III trials [5–7, 15], the treatment of subsequent relapses beyond the first recurrence remains a formidable challenge considering the lack of well-designed and controlled studies. In this retrospective analysis, we characterized in a large cohort of 1620 patients the heterogeneous chemotherapeutic regimens used in subsequent relapses of ovarian cancer. We were able to show an increasing use of nonplatinum monochemotherapies with increasing therapy line. By evaluating the second-line therapy in detail, we could point out that at least 20% of patients with platinum-resistant disease and 46% of patients with sensitive disease did not receive a treatment, considered today as ‘state of the art’ therapy [16]. These data are in line with the results of a quality survey of the AGO in Germany [17] that revealed an adherence to the latest treatment recommendations in only 50% of the second-line patients. Currently, there is very little information on the benefit of treatment of subsequent recurrences beyond the second-line treatment. Only a few small retrospective studies do provide some insight in treatment modalities and efficacy after the second relapse [18, 19]. The only randomized trial that has revealed an increased PFS and OS for the third-line chemotherapy by comparing PLD or topotecan to canfosfamide was reported by Vergote et al. [20]. In our study, PFS after the first recurrence was about 10 months, decreasing from 6 to 4 months for the second to fifth recurrence. Hence, the second-line survival rates are similar to several randomized trials presenting a PFS of 5–12 months [5–7]. The PFS of

Figure 1. Distribution of (A) mono- and (B) polychemotherapeutic regimens according to platinum sensitivity.
patients experiencing further relapses are comparable to studies dealing with platinum-resistant disease [21]. The OS rates after the first recurrence was about 17 months, falling from 11 to 5 months from further relapse similar to the results of a small study conducted by Hoskins et al. [10]. Regarding these short survival periods after the fourth recurrence and response rates of only 10–20% in platinum-resistant/refractory disease reported by others [22–24], the indication for chemotherapy in these women seems questionable. Moreover, other authors were able to point out a lack of survival advantage by giving additional therapies [25]. However, the most patients prefer subsequent chemotherapy even when only gaining a small survival benefit [26, 27]. In a study from Donovan et al., the patients accepted to achieve a cytotoxic therapy even with an anticipated median OS of less than 1 week [28]. Here, we were able to show a distinct impact of subsequent relapse treatment on PFS and OS. Both in third and fourth line therapy, there was a PFS gain of 3.5 months for patients receiving relapse treatment compared with patients without any treatment. Furthermore, there was a significant OS gain in the third, fourth and fifth line treatment of 10.1, 7.3, and 4.3 months, respectively. These data suggest that multiple retreatments can be effective in certain patients and should, therefore, be considered [29]. On the other hand, our results point out that the application of three lines of relapse treatment seems to be the maximum acceptable therapy. Higher lines of subsequent treatment seem not to be beneficial for these patients.

This study has several strengths and limitations. A major strength of this trial is the large number of patients in a well-characterized cohort. All patients received a similar platinum-based combination therapy, which showed comparable potency and had frequent follow-up visits. Therefore, the data could be pooled for this analysis. Nevertheless, this study is a retrospective analysis of prospectively collected data and some individual patients’ data are missing. Because of the underlying three subsequent prospective trials, there was a large time

Figure 2. Kaplan–Meier analyses of progression-free survival (PFS) and overall survival (OS) were carried out in the whole patients’ cohort depending on subsequent relapse. Panel A shows PFS after relapse 1–5. Panel B shows OS after relapse 1–5.
interval of accrual. A selection bias can therefore not been excluded and the data need to be interpreted carefully especially for treatment comparisons.

Presently, the only clearly established prognostic factor after recurrence is the treatment-free interval from first-line treatment to relapse [30–32]. Nevertheless, the resulting definitions of platinum sensitivity (i.e. sensitive/resistant/refractory) are derived for women after first-line therapy. Therefore, we analyzed the impact of standard clinical factors at higher relapses. Our data strongly support the prognostic significance of platinum sensitivity in subsequent relapses up to third relapse. Furthermore, we could point out that optimal tumor debulking at primary operation (i.e. no residual tumor) is associated with a significant longer PFS and OS in the second and third line therapies. These results are in line with the established insights from first-line treatment [4]. However, our findings are in contrast to a small trial by Harrison et al. [33]. These authors showed that optimal tumor debulking at primary operation is not a prognostic factor for PFS after first relapse. In this study, only patients experiencing a complete response after the second-line treatment were included. In a larger study by Hoskins et al., tumor residuals after primary debulking surgery did not show a prognostic impact at second relapse either [34]. This trial had its limitation in the low amount of optimal debulked patients. Contrary to this, our study comprised about 25% patients without residual tumor after primary surgery. Therefore, the effect of radical debulking could have become more evident in our trial. Recently, some authors showed that the duration of subsequent response is very rarely longer than the duration of response before [32, 35]. This effect might lead to a shortened PFS in suboptimally debulked patients experiencing subsequent recurrences. However, residual disease at primary operation retained its prognostic impact for higher lines in multivariate analysis. In conclusion, we could point out that subsequent retreatment in relapsed ovarian cancer can prolong PFS and OS in selected

Figure 3. Kaplan–Meier analyses of progression-free survival (PFS) and overall survival (OS) depending on subsequent relapse according to treatment decision at relapse. Panel A shows PFS after relapse 2–4 stratified by the patients that did receive relapse treatment and the patients that did not receive treatment anymore. Panel B shows corresponding OS.
patients up to the fifth line. We were able to follow up a large amount of women up to the sixth-line therapy. Even a maximum of nine relapse therapies in one patient were noted. Nevertheless, a routine treatment after the fourth relapse seems not beneficial anymore. Most standard prognostic factors failed at higher recurrences. Platinum sensitivity and postoperative residual tumor after first-line treatment might help to identify the patients, who will benefit from subsequent relapse treatment. Clearly, the selection bias of our trial should cause us to a careful interpretation of these data. To better describe the benefits, symptom control and response rates should be integrated in future studies. Furthermore, it may be that factors identified at the time of recurrence could be more predictive.

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**Disclosures**

The authors have declared no conflicts of interest.

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