Advanced Epithelial Ovarian Cancer in the Elderly: Chemotherapy Tolerance and Outcome

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Abstract. Background: The prognostic significance of age in ovarian cancer has not been clarified. We investigated the characteristics of ovarian cancer presenting in ages >70 years and assessed the prognostic significance of advanced age. Patients and Methods: Four hundred and fifty-three patients with stage IIC-IV ovarian cancer (age>70 years n=106 [23%]), treated postoperatively with platinum-based chemotherapy were retrospectively reviewed. Results: Median overall survival (OS) of patients ≤70 years old (52.3 months, 95% CI: 43.2-61.3) was longer than that of older patients (38.8 months, 95% CI: 29.9-47.7) (p=0.005), but this difference was not significant in a multivariate analysis (p=0.978). Age >70 years was correlated with worse performance status (PS) (p=0.019), higher tumor grade (p=0.033), residual disease >2 cm (p=0.006) and less frequent paclitaxel administration (p<0.001). Toxicity from chemotherapy was similar between the two age groups, but the relative dose intensity of paclitaxel was lower among elderly patients. Conclusion: The worse outcome of ovarian cancer in elderly patients may be attributed to other associated adverse prognostic factors, but advanced age was not an independent prognostic factor.

Epithelial ovarian cancer (EOC) is predominantly a disease of the elderly. Its incidence increases sharply with age and about half of all ovarian cancers occur in women older than 65 (1, 2). Elderly patients with cancer represent a rapidly growing population in the USA and Europe (2). This increase in the numbers of elderly patients alters the demographics of cancer and highlights the need to develop more age-oriented treatment strategies. Although elderly patients form the majority of cancer patients, few studies have specifically focused on this population and the results of these studies are, in many cases, contradictory. Some studies including elderly patients with cancer have shown that elderly patients may tolerate treatment poorly (3-5), while other studies showed that they may benefit younger patients as well, and have similar survival rates (6, 7).

Systemic chemotherapy is effective in EOC, but cure is rare in advanced FIGO stages (IIC-IV). The current standard in these stages is optimal cytoreductive surgery followed by chemotherapy using a combination of a platinum compound with paclitaxel (8-11). Although survival of patients with ovarian cancer has generally improved during the last decades, such improvement has not been shown for elderly women (12). The reasons for this difference are not clear. Advanced age has been reported to be an independent adverse prognostic factor (13, 14), although no such association was found in a recent analysis for patients receiving second-line chemotherapy (15). In addition, several important prognostic factors, such as stage at diagnosis and surgical management have been reported to significantly differ between elderly and younger patients (14, 16, 17), and this might account for the differences in prognosis.

In order to address these issues, we report our experience regarding treatment and prognosis in elderly patients with FIGO stages IIC-IV EOC.

Patients and Methods

Patients. Our EOC database, which includes patients receiving first-line chemotherapy in our Department since April 1994, was analysed selecting only patients with FIGO stages IIC-IV. Patients were stratified according to age into two groups: patients aged ≤70 years and patients >70 years. Patients who received their first course of chemotherapy up to June 2004 were included, in order to ensure at least one year of follow-up, since our database was updated in June 2005.

All patients were older than 18 years, with histologically or cytologically proven EOC. Patients with borderline or germ cell tumors were excluded from the analysis. Creatinine clearance was
calculated according the Cockroft Formula (18), while carboplatin dose was calculated according to the Calvert formula (19).

Staging was performed according to the FIGO staging system. Residual disease after surgical debulking was recorded according to the assessment by the surgeon. Tumor grading and histology were determined according to current FIGO guidelines. Performance status was evaluated according to the ECOG standards immediately before the initiation of chemotherapy.

Following surgery, all patients received platinum-based chemotherapy. After the completion of chemotherapy, follow-up included a clinical examination and serum CA125 assay quarterly for the first two years, biannually for the following 3 years and annually thereafter. Chest X-ray and CT scan of the abdomen and the pelvis were performed every 6 months for the first 5 years and annually thereafter. Investigations were performed earlier if clinically indicated.

**Efficacy and toxicity analysis.** Survival was calculated from the day of the initiation of treatment until date of death or last contact for patients still alive at the time of follow-up. In an intention-to-treat analysis all patients were included in survival analysis. Patients with bidimensionally measurable disease and having at least one follow-up tumor assessment were eligible for response evaluation. Standard WHO criteria (20) were used for classifying response. Toxicity was evaluated at each chemotherapy visit according to National Cancer Institute Common Toxicity Criteria. All patients who received at least one cycle of chemotherapy were included in the toxicity analysis. Relative dose intensity (RDI) was defined as the percentage of the expected dose administered to the patient (per unit of time expressed in mg/m²/week).

**Statistical analysis.** All analyses were performed using the SPSS statistical software (SPSS for Windows, version 10, SPSS Inc., Chicago, IL, USA). Frequency distributions were used to describe the categorical variables, whereas continuous variables were presented as means and standard deviations. Differences across treatment arms regarding all categorical variables were examined with a χ² test whereas the Student’s t-test was used to test the equality of the appropriate means for continuous variables. The independent significance of the association of baseline characteristics with the age groups was tested using logistic regression analysis.

Survival curves were produced with the Kaplan Meier method (21) and compared between arms with the log-rank test. For univariate and multivariate analyses of survival, the Cox proportional hazards model was used (22). Factors with a p-value <0.1 in the multivariate analysis were entered in a multivariate Cox regression model. Throughout the analysis a level of 5% was used to denote statistical significance except as indicated.

### Results

**Baseline characteristics.** Four hundred and fifty-three consecutive patients with stage IIC-IV ovarian carcinoma or peritoneal carcinomatosis, who were operated on in our institution and received postoperative chemotherapy in our Department from April 1994 to June 2004, were included in this analysis. One-hundred and six patients (23.4%) were older than 70 years.

<table>
<thead>
<tr>
<th>Table I. Patient characteristics.</th>
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<tr>
<td>Age group</td>
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<tr>
<td>≤70</td>
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<td>≥70</td>
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| No. of patients | 453 | 106 |
| ECOG PS | 0.001 |
| Grade | 0.005 |
| Residual disease | <0.001 |
| Histology | 0.600 |
| Baseline Hb | 0.938 |
| First-line chemotherapy | <0.001 |
| PS: performance status; Hb: hemoglobin (g/dl); Cy: cyclophosphamide; P: cisplatin; C: carboplatin; T: paclitaxel; E: epirubicin; I: ifosfamide; A: Adriamycin; *: p-value was determined by χ² test.

**Patient characteristics according to age are shown in Table I.** The median age of the elderly group was 75 years, while that of the younger group was 57 years. Comparison between the two age groups showed significant differences in the distribution of ECOG PS (p<0.001), tumor grade (p=0.005) and residual disease after surgical debulking (p<0.001). Specifically, patients over 70 years of age were more likely to have ECOG PS ≥1 (54.3% vs. 30.8%), less likely to have...
Grade 1 tumors (1% vs. 8.4%) and the quality of their surgical debulking was inferior to that of their younger counterparts (residual disease <2 cm in 12.3% vs. 29.2%).

The treatment administered also differed significantly between the two age groups: younger patients were more likely to receive paclitaxel-containing chemotherapy (94.8% vs. 73.2%, \( p<0.001 \)), while more older patients received carboplatin monotherapy (20.1% vs. 3.4%). On the contrary, there were no significant differences regarding tumor stage or histology. Logistic regression analysis showed that the association of age groups with PS (0 vs. ≥1, \( p=0.019 \)), tumor grade (1, 2 vs. 3, \( p=0.033 \)), residual disease (0-2 cm vs. >2 cm, \( p=0.006 \)) and paclitaxel administration (yes vs. no, \( p<0.001 \)) retained their statistical significance.

Chemotherapy administration and tolerance. The treatment administered to the patients included in the analysis is shown in Table I. Since 96.8% of patients ≤70 years received paclitaxel-containing chemotherapy, meaningful comparisons of exposure to chemotherapy and toxicity between the two age groups could be performed only for this treatment.

The mean number of cycles did not differ significantly between the two age groups (Table II). Nevertheless, the mean RDI of paclitaxel differed significantly among patients treated with paclitaxel/carboplatin combination (95.3% vs. 90%, \( p=0.026 \)). Within this group, 51% of elderly patients received 100% of the expected paclitaxel RDI compared to that received by 69% of younger patients. The RDI of the other agents were similar in the two age groups.

The most frequently recorded toxicities are shown in Table III. There were no significant differences between the two age groups apart from grade 3 allergy: there were two cases among patients <70 years old, compared to no cases among older women (\( p=0.006 \)).

Survival and progression-free survival (PFS). Two hundred and ninety-one patients were evaluable for response to first-line chemotherapy: 216 among patients ≤70 years of age and 75 among patients >70 years of age. Overall response rates (complete and partial responses) were similar: 79% for patients ≤70 and 71% for patients >70 (\( p=0.156 \)).

After a median follow up of 59 months, median OS and PFS of the whole population were 49.9 months (95% CI: 44.2-55.6 months) and 20.6 months (95% CI: 17.5-23.7 months), respectively. Median OS of patients ≤70 years old (52.3 months, 95% CI: 43.2-61.3 months) was significantly longer than that of older patients (38.8 months, 95% CI: 29.9-47.7 months) (\( p=0.005 \)) (Figure 1a). On the contrary, PFS did not differ significantly between the two age groups (21.2 months [95% CI: 17.4-24.9 months] vs. 16.7 months [95% CI: 12.5-20.9 months], \( p=0.071 \)) (Figure 1b).

Univariate analysis of the whole population identified residual disease (0-2 cm vs. >2 cm, \( p<0.001 \)), ECOG PS (0 vs. ≥1, \( p<0.001 \)), histological type (mucinous+clear cell vs. other histologies, \( p=0.038 \)) and treatment with paclitaxel (\( p=0.005 \)) as being the factors associated with OS, apart
from age groups. On the contrary, tumor grade (1, 2 vs. 3, \( p=0.556 \)) was not associated with prognosis.

Multivariate analysis including residual disease, PS, type of chemotherapy, histological type, stage and age showed that residual disease >2 cm, paclitaxel-containing chemotherapy, PS>0, stage IV and mucinous or clear cell type were independently associated with inferior survival (Table IV). Residual disease \( (p<0.001) \), PS \( (p<0.001) \), type of chemotherapy \( (p=0.036) \) and stage \( (p=0.008) \) were also independently associated with PFS. Age >70 years did not show an independent association either with OS \( (p=0.978) \) or with PFS \( (p=0.556) \).

Stratified analyses. In order to assess the value of age as a prognostic factor within specific subgroups of patients, further analysis was performed after stratification according to tumor grade, residual disease, histology, stage, type of chemotherapy and PS. These factors were categorized as previously mentioned for the univariate and multivariate analysis of the whole population. Log rank test showed that age <70 years was associated with inferior survival only in the subgroup of tumor grade 1 or 2 \( (p=0.028) \). Nevertheless, the age group did not retain its prognostic significance \( (p=0.401) \), when it was included in a multivariate Cox regression analysis model with residual disease, PS and stage.

Prognostic factors among patients >70 years of age. During a median follow up of 63 months, 70 patients relapsed and 67 patients died due to disease progression among those patients >70 years of age. Univariate analysis showed that the type of chemotherapy \( (p=0.003) \), PS \( (p<0.001) \) and stage \( (p=0.050) \) were associated with survival, while PS \( (p=0.001) \) was the only factor associated with PFS. Residual disease \( (p=0.222) \) and histology \( (p=0.333) \) were not

Table IV. Univariate and multivariate analysis of factors associated with survival.

<table>
<thead>
<tr>
<th></th>
<th>MS (95% CI)</th>
<th>Univariate</th>
<th>Multivariate</th>
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<tbody>
<tr>
<td></td>
<td>(months)</td>
<td>( P )</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;70 (n=105)</td>
<td>38.8 (29.9-47.7)</td>
<td>0.005 1</td>
<td>1</td>
</tr>
<tr>
<td>( \leq 70 ) (n=347)</td>
<td>52.3 (43.2-61.3)</td>
<td>1 (0.73-1.37)</td>
<td>0.978</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
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<tr>
<td>Stage IIC, III (n=373)</td>
<td>52.7 (44.7-60.7)</td>
<td>&lt;0.001 1</td>
<td>1</td>
</tr>
<tr>
<td>Stage IV (n=79)</td>
<td>24.9 (8.2-41.7)</td>
<td>1.45 (1.05-2)</td>
<td>0.026</td>
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<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
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<tr>
<td>PS=0 (n=288)</td>
<td>74.8 (58.9-90.8)</td>
<td>&lt;0.001 1</td>
<td>1</td>
</tr>
<tr>
<td>PS( \geq 1 ) (n=164)</td>
<td>24.6 (17.3-31.8)</td>
<td>2.2 (1.67-2.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Residual</td>
<td></td>
<td></td>
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<tr>
<td>0-2 cm (n=114)</td>
<td>NR</td>
<td>&lt;0.001 1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;2 cm (n=337)</td>
<td>40 (33.3-46.8)</td>
<td>2.14 (1.42-3.2)</td>
<td></td>
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<tr>
<td>Histology</td>
<td></td>
<td></td>
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<tr>
<td>M+C (n=44)</td>
<td>22 (7.1-36.8)</td>
<td>0.038 1</td>
<td>0.013</td>
</tr>
<tr>
<td>Other (n=407)</td>
<td>50 (44.5-57.6)</td>
<td>0.59 (0.4-0.87)</td>
<td></td>
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<tr>
<td>Paclitaxel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n=41)</td>
<td>22 (3.1-40.7)</td>
<td>0.002 1</td>
<td>0.006</td>
</tr>
<tr>
<td>Yes (n=409)</td>
<td>51.1 (43.5-59.2)</td>
<td>0.54 (0.36-0.8)</td>
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</tbody>
</table>

MS: median survival; NR: not reached; M: mucinous; C: clear cell; HR: hazard ratio.

Figure 1. Kaplan-Meier overall survival (a) and progression-free survival (b) curves of 451 patients with advanced ovarian carcinoma according to age. Overall survival was significantly longer for patients \( \leq 70 \) years of age (log-rank \( p=0.005 \)), but progression-free survival was not (log-rank \( p=0.071 \)).
associated with prognosis. Categorisation of these factors was similar to that used for the analysis in the whole population. Multivariate analysis showed that only PS 0 (HR: 0.43, 95% CI: 0.26–0.73, p=0.001) and inclusion of paclitaxel in the chemotherapy regimen (HR: 0.47, 95% CI: 0.27–0.81, p=0.009) were independently associated with improved prognosis.

Discussion

Ovarian cancer is a disease of elderly women. It has been speculated that age can affect prognosis in ovarian cancer in two ways: an independent but yet unexplained association of advanced age with prognosis, possibly due to different tumor biology (23), and a more conservative therapeutic approach, which may result in inferior surgical debulking (14, 16) and lower exposure to modern chemotherapy (14, 17, 24). The latter could be particularly relevant to the administration of novel agents and especially paclitaxel, which has been shown to prolong survival in patients with advanced ovarian cancer (8, 9).

We attempted to address these issues by comparing chemotherapy tolerance and outcome between two age groups: >70 and ≤70 years old. Our population was homogenous regarding stage and management, since we only selected stages IIC-IV, while surgery in all cases was performed in our institution, which is a referral center for gynaecological malignancies, with significant experience in the management of ovarian cancer. Furthermore, the follow-up protocol for all patients with ovarian cancer is the same regardless of inclusion in clinical trials.

A major limitation of our analysis is its retrospective nature. We attempted to overcome this by performing multivariate and stratified analyses, although we acknowledge that a prospective trial with age as a variable is the most appropriate methodology to address the issue in question. Nevertheless, we believe that our results are clinically relevant.

In accordance with other reports, elderly women were found to have an inferior outcome compared to younger patients. Nevertheless, our results do not support an independent association of advanced age with prognosis, but rather an association with adverse prognostic factors and differences in management, which could account for the inferior outcome of elderly patients. We showed an independent association of age >70 years with worse PS and higher tumor grade. Similar findings have also been reported by others (13), although the association with tumor grade has been challenged by some studies (16). Both these factors have been associated with inferior survival in ovarian carcinoma (13, 16), although only PS was an independent prognostic factor in our series.

The quality of debulking surgery is a well established powerful prognostic factor (25) and was found to be inferior among elderly patients in our study. This is in line with several other reports (14, 16, 23, 26), although the reason for this is not clear. Advanced stage at presentation might explain this difference between young and elderly women, although this is not relevant for our analysis, since we only included patients with advanced stages. Another possible explanation is that the surgical care pattern is influenced by the fear of higher morbidity and mortality due to the high prevalence of comorbidities in this age group. Although this may have been true in the past, recent developments in the field of anesthesiology, perioperative care and surgical techniques have reduced the rate of complications considerably, even in patients with comorbid illnesses (27, 28). We believe that differences in the quality of debulking surgery is probably the most important reason for the inferior outcome of elderly patients. Based on data from contemporary surgical series, maximal surgical effort should be applied to elderly women equally aggressively as in younger patients.

Another significant finding in the management of these patients was the lower exposure of elderly women to paclitaxel. Fewer patients older than 70 were treated with paclitaxel. Furthermore, within the group of patients who were treated with paclitaxel, mean RDI of this agent was lower among women over 70 years of age, while the mean RDI of the other agents was similar. This indicates more frequent paclitaxel dose reductions in elderly women. This has also been shown in a recent retrospective analysis of 148 Italian patients (29), especially for patients older than 75 years of age. Although it could be argued that these reductions were justified by increased toxicity, this was not found in our study. Therefore, it could be speculated that there is a lower threshold for reducing paclitaxel dose in anticipation of serious toxicity rather than when toxicity actually occurs. This attitude is not supported by our toxicity analysis nor from recent data from a smaller series (30) suggesting that standard doses of paclitaxel-containing chemotherapy can be safely administered to elderly patients.

We found that elderly patients tolerated platinum and paclitaxel-based chemotherapy as well as their younger counterparts. Specifically, hematological toxicity and neurotoxicity were not more frequent among elderly patients. Nevertheless, this result is confounded by the lower exposure of this age group to paclitaxel. We believe that elderly patients with advanced ovarian cancer should be offered standard chemotherapy.

More research is necessary in order to identify patients at high-risk of developing serious toxicity from this treatment. These patients could be offered carboplatin monotherapy, since its efficacy has been proven in the recent ICON 3 study, showing comparable survival to carboplatin-paclitaxel combination (31).

We did not find an independent association of age with prognosis, which is in contrast with previous reports,
indicating that advanced age is an independent predictor of poor prognosis (13, 32). These data came from the retrospective analysis of more than 2000 patients treated with chemotherapy within the context of successive multicenter randomized trials. The age of 70 was also used to define the "elderly" group. It is possible that the difference in prognosis did not reach statistical significance due to the lower number of patients included in our study. Nevertheless, a p-value of 0.978 and 95% CI ranging from 0.73 to 1.37 make this possibility unlikely. Furthermore, the age group was not an independent prognostic factor in any of the subgroups analysed.

A more important difference between the aforementioned studies and ours is the treatment received by the patients included in these analyses: no paclitaxel was administered in the previous studies, while the majority of our patients (90%) received paclitaxel-containing chemotherapy. Whether paclitaxel administration may have affected the prognostic significance of age cannot be answered by data available so far. The addition of paclitaxel prolongs survival compared to the combination of cyclophosphamide and cisplatin (8, 9). This is also reflected in our results, although indirect comparisons should be viewed with caution: the median survival of our patients with residual disease >2 cm was 40 months compared to 21 months or less for patients with residual disease >3 cm, reported in one previous study (13). As with our results, age was not found to be an independent prognostic factor in a recent analysis of 889 patients included in the SCOTROC-1 trial (33). All these patients received paclitaxel or docetaxel. However, it should be mentioned that this analysis did not specifically evaluate the prognostic significance of age.

Molecular differences between different age groups should also be taken into account in order to explain this inconsistency of the results. Mutations of BRCA1 and BRCA2 genes, which predispose to hereditary breast and ovarian cancer occur more frequently in younger women (34) and have been associated with better prognosis (35). More importantly, preclinical data have suggested a different chemosensitivity profile between the taxanes and older agents, such as cisplatin and adriamycin, depending on the expression of the BRCA1 and BRCA2 genes (36, 37).

Conclusion

Patients older than 70 years with advanced EOC have an inferior outcome compared to younger patients, which can be explained by the association of advanced age with adverse prognostic factors, but its significance as an independent prognostic factor is not supported by our results. Furthermore, a more conservative approach is usually adopted for these patients, reflected by less frequent optimal debulking surgery, less frequent use of paclitaxel and a lower threshold for paclitaxel dose reduction. These differences in their management are not justified by our results, which showed good tolerance of platinum-paclitaxel therapy by older patients. We, therefore, believe that surgical and medical management of elderly women should be similar to that of younger women and this could result in improvement of their prognosis.

References


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