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Early treatment modifications improve chemotherapy adherence in ovarian cancer patients ≥70 years

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HIGHLIGHTS

- Ovarian cancer patients ≥70 years show an impaired survival prognosis compared to younger patients.
- Elderly patients benefit from an application of >4 cycles of a platinum/taxane-based chemotherapy.
- Performance of cycle delays increase the chance of completing >4 cycles of chemotherapy among elderly patients.
- Most reasons for early treatment discontinuation are likely to be influenceable by treatment modifications.

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ABSTRACT

Objective. Elderly ovarian cancer patients are underrepresented in clinical trials and disadvantaged with regard to therapeutic standards compared to other age groups. We explored the specific performance of a subset of patients aged ≥70 years in a large meta-data set of 3 phase III trials.

Methods. 3333 patients with advanced ovarian cancer recruited into 3 clinical phase III trials of the AGO & GINECO study groups were retrospectively analysed for age-specific prognostic and toxicity parameters.

Results. Only 10% (359/3333) of the patients were aged ≥70 years. This subgroup presented with impaired performance statuses (ECOG 2 14.8 vs 10.1%) and higher FIGO-stages (FIGO IIIC-IV 78.5 vs 73.6%) compared to younger patients. Complete operative tumor resection was achieved less frequently (postoperative tumor burden >10 mm 46.7 vs 33.9%) and elderly received less cycles of platinum/taxane-based chemotherapies (>4 cycles 81.9 vs 90.7%). FIGO-stage, histology, postoperative tumor burden and number of chemotherapy cycles were independent prognostic factors in elderly patients. Elderly patients with ≤4 cycles of chemotherapy showed a median OS of 18.4 months compared to 30.9 months in elderly with 5–6 cycles ($p < 0.001$). This effect was accentuated in elderly patients after complete tumor resection (cumulative survival benefit of 33.8 months). Analyses of chemotherapeutic delivery revealed that elderly patients with at least one cycle delay had higher chances to complete >4 cycles of chemotherapy.

Conclusions. Protocol defined treatment modifications might support completion of >4 cycles of standard chemotherapy in fit elderly OC patients.

1. Objective

Age per se is a strong prognostic factor in ovarian cancer (OC) [1,2]. The average age of patients upon diagnosis is 63 years and, due to the increasing life expectancy of women in the Western world, patients in advanced age represent the fastest-growing group of patients with OC [3]. A distinct reservation concerning the appropriate treatment in the

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group of aged patients prevails although a comparable tolerability towards therapy related adverse effects and a comparable therapeutic benefit has been described [4,5]. Tolerability, comorbidity and investigators` concerns were shown to be major causes for a non-guideline adherent therapeutic management of elderly patients [6]. Whereas optimizations in the standard of care of OC treatment improved prognoses for all other age groups the prognosis in elderly patients is still poor [3,7]. So far, age-specific analyses of prognostic factors specifically in elderly patients are rare and separately focus either on the impact of the surgical management or the feasibility of cytostatic therapies [8,9,10].

This exploratory analysis of 3 first-line chemotherapy phase III studies in advanced ovarian cancer investigated the specific performance of patients ≥70 years under clinical trial conditions with age-specific prognostic and toxicity parameters in a meta data set of 3333 patients [11–13].

2. Patients and methods

2.1. Data set

This joint retrospective and explorative analysis is based on individual patients data sets of 3 randomized phase III trials led by the AGO (Arbeitsgemeinschaft Gynaekologische Onkologie)-Ovar Study Group. All patients presented with advanced epithelian ovarian cancer (FIGO IIB-IV) and were planned to receive at least 6 courses of chemotherapy after initial cytoreductive surgery. The clinical studies were performed by the AGO study group (Germany) together with GINECO (Groupe d'Investigateurs Nationaux pour l'Étude des Cancers Ovariens et du sein) from France between 1995 and 2002 and involved the following treatment arms:

- AGO-OVAR 3 (Carboplatin/Paclitaxel vs. Cisplatin/Paclitaxel)
- AGO-OVAR 5 (Carboplatin/Paclitaxel vs. Epirubicin/Carboplatin/Paclitaxel)
- AGO-OVAR 7 (Carboplatin/Paclitaxel vs. Carboplatin/Paclitaxel → Topotecan)

All trials are published and results were reported and discussed in detail elsewhere [11–13]. The inclusion and exclusion criteria were mostly identical in all 3 trials, in particular without an age specific exclusion of elderly patients: a clinical performance status of at least ECOG 2 and adequate serum levels for hematologic, renal and hepatic parameters were required. Pathology was centrally reviewed in a subset. All patients underwent upfront surgery followed by systemic drug therapies consisting of a platinum- and taxane-based chemotherapy ± an optional study drug. 50% on the patients in all age groups were recruited either in the platinum/taxane control arms and 50% in the experimental arms (for details see Supplementary Table 1A and B). As a basis for further data interpretation, none of these trials showed any significant differences for the variant treatment arms with respect to Progression Free Survival (PFS) or Overall Survival (OS). Data were retrieved from the study centre from the original case reports. Quality controls included data source verification by monitoring, double data entry and in-house monitoring in the central study office. Surgical and pathology reports were reviewed. The protocols were approved by local ethical committees and adhered to the declaration of Helsinki.

2.2. Patients

3373 were randomized in the respective studies and a total number of 3333 patients who received at least one cycle of the assigned chemotherapeutic regimen were included into this age specific analysis. 40 patients were excluded after stratification and randomization: 37 patients received 0 cycles (n = 4 AGO OVAR 3, n = 16 AGO OVAR 5, n = 16 AGO OVAR 7, n = 1 no report) and 3 patients did not have an adequate FIGO stage (FIGO IB: n = 2 AGO OVAR 5 + 7, FIGO IIA: n = 1 AGO OVAR 7).

2.3. Dichotomization and statistics

Based on prior AGO/GINECO studies addressing elderly patients' tolerance towards therapy related toxicities [6,16,17,20,26] the dichotomization of the patient cohort was adjusted on the rationale of the patients' age at the time of registration in either group <70 years or ≥70 years. We analysed the individual prognostic factors and their association with the patients' age using contingency tables. The selection of prognostic factors was based on the AGO first-line meta data set and included patient characteristics (Eastern Cooperative Oncology Group (ECOG), body mass index (BMI)), disease related factors (Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) classification, residual tumor after surgery), tumor biology and treatment delivery (number of treatment cycles, protocol defined dose reductions and cycle delays of >14 days). Toxicities were documented and evaluated according to the NCI Common Toxicity Criteria version 2.0.

Statistical significances were determined by chi-square tests and confirmed by the Fisher exact test. PFS and OS were calculated from randomization to the day on which the first recurrence or progression or death was observed and documented. For patients without tumor recurrence or death by the end of the study PFS and OS were calculated from the time of registration until the last visit within the study setting. Survival analyses for PFS and OS were performed by Kaplan-Meier estimates and log-rank tests. Multivariate Cox regression analysis evaluated the independent age-specific prognostic factors for PFS and OS. All statistical analyses were performed using SPSS statistical software version 18.0. p-Values < 0.05 were considered significant.

However, due to the retrospective design of the study, all results should be interpreted as hypothesis generating only.

3. Results

3.1. Age distribution

Mean age of the evaluated patient cohort was 58 years with a range from 19 to 84 years. At time of registration 2974 (89.2%) patients were younger than 70 years and 359 (10.8%) were ≥70 years of age. In the group of the “elderly” (≥70 years) most of the patients were between 70 and 75 years of age (n = 278). 75 patients were between 75 and 80 years and only 6 patients were ≥80 years of age. Median age was 55 years for the patients <70 years and 73 years for the patients ≥70 years.

3.2. Patient and therapy characteristics

Significant differences in survival prognoses were found between the age groups. The median PFS was 23.0 months and OS 45.9 months in patients <70 years, whereas the PFS and OS in elderly patients were only 18.4 months and 29.6 months, respectively (Table 1, Fig. 1A). Both age groups differed regarding the initial ECOG performance status and BMI. Elderly patients were diagnosed with higher FIGO stages. The biologic subtype of the disease did not show age-specific significant differences. Almost half of elderly patients had a residual tumor burden of >1 cm after cytoreductive surgery (p < 0.001). Elderly patients received less cycles of chemotherapy compared to their younger counterparts (p < 0.001) (Table 1). Particularly, <5 cycles of the assigned chemotherapy were delivered in 18% of the elderly patients which was twice as often as in patients <70 years. No age specific differences were found regarding chemotherapeutic dose reductions or cycle delays. No age-specific differences for reasons of death were observed.

Table 1
Clinically relevant patients' characteristics at initial presentation and over the course of therapy divided by age groups dichotomized at 70 years. p-Values < 0.05 were considered significant.

Patient and therapy characteristics		<70 years	≥70 years	Total	
		n (%)	n (%)	n (%)	p-Value
Total number of patients		2974 (89)	359 (10.8)	3333	
Performance status	ECOG 0	1157 (39.1)	104 (29.1)	1261 (33.1)	<0.001
	ECOG 1	1497(50.6)	201 (56.1)	1698 (51.3)	
	ECOG 2	299 (10.1)	53 (14.8)	352 (10.6)	
Body Mass Index	<19	318 (10.7)	27 (7.5)	345 (10.4)	0.039
	19–24	1347 (45.3)	185 (51.5)	1532 (46.0)	
	>24	1306 (43.9)	147 (40.9)	1453 (43.6)	
FIGO stage	IIB–IIIB	788 (26.6)	77 (21.5)	865 (26.0)	0.041
	IIIC–IV	2180 (73.6)	281 (78.5)	2461 (74.0)	
Histologic subtypes	Serous papillary	2114 (71.1)	258 (71.9)	2372 (71.2)	0.557
	Endometrioid	262 (8.8)	23 (6.4)	285 (8.6)	
	Mucinous	131 (4.4)	18 (4.5)	149 (4.5)	
	Others	465 (15.7)	60 (16.7)	525 (15.8)	
Postoperative tumor burden	0 mm	1024 (34.9)	85 (24.1)	1109 (33.8)	<0.001
	1–10 mm	915 (31.2)	103 (29.2)	1018 (31.0)	
	>10 mm	992 (33.9)	165 (46.7)	1157 (35.2)	
Number of treatment cycles	≤4 cycles	275 (9.2)	65 (18.1)	340 (10.2)	<0.001
	5–6 cycles	1958 (65.8)	224 (62.4)	2182 (65.5)	
	>6 cycles	741 (24.9)	70 (19.5)	811 (24.2)	
Dose reductions	Yes	426 (14.3)	64 (17.9)	490 (14.7)	0.082
	No	2548 (85.7)	295 (82.2)	2843 (85.3)	
Cycle delays	Yes	1871/62.9)	231 (64.3)	2102 (63.1)	0.643
	No	1103 (37.1)	128 (35.7)	1231 (36.9)	
Survival prognoses	***PFS in months*** *(95% CI)*	***23.8*** *(22.6–25.1)*	***18.4*** *(16.2–20.5)*	***23.1*** *(22.0–24.1)*	***<0.001***
	OS in months *(95% CI)*	***45.9*** *(43.7–48.1)*	***29.6*** *(25.6–33.5)*	***44.1*** *(42.1–46.2)*	***<0.001***
Reasons for deaths	Cancer-related	1612 (94.5)	232 (92.1)	1844 (94.2)	n.s.
	Treatment-related	7 (<1)	4 (1.6)	11 (0.6)	
	Others	86 (5.0)	16 (6.3)	102 (5.2)	

3.3. Univariate prognosis analyses in elderly patients (≥70 years)

Patients and tumor characteristics in patients ≥70 years were examined separately. Interestingly, no association of ECOG-status and BMI was found with survival data, while the mucinous biologic subtype was associated with lowered life expectancies (Table 2). Tumor residua after upfront surgery were also associated with poor survival in elderly (Fig. 1C). With regard to the chemotherapeutic delivery application of <5 cycles of platinum-/taxane based chemotherapies led to drastically impaired prognoses, while dose reductions and cycle delays did not significantly impact the prognosis (Fig. 1D and Table 2).

3.4. Multivariate regression analyses for PFS and OS of patients ≥70 years

Underweight, higher FIGO stages, mucinous tumor subtype, residual tumor size and number of received chemotherapy cycles were determined as independent prognostic factors in elderly patients, while the ECOG status did not significantly impact the survival (Table 3). Again, application of <5 cycles of a platin-/taxane based chemotherapy led to an impaired survival prognosis with a hazard ratio of 2.3 for PFS and 2.1 for OS (both $p < 0.001$).

3.5. Age specific PFS and OS according to both age groups depending on "optimal treatment"

To further explore the prognostic potential of combined surgical and chemotherapeutic treatment variables a pooled analysis for the "optimal treatment" was performed in both age groups. The optimal treatment was defined as a surgery with complete resection (residual tumor = 0 cm) and an application of at least 5 cycles of platinum/taxane-based chemotherapies regardless of modifications of delivery such as dose reductions or cycle delays. Only 20% (71/359pts) of the elderly patients fulfilled these criteria and showed a PFS of 33.3 and an OS of 58.7 months compared to a median PFS of 54.0 and an OS of 87.1 months in younger optimally treated patients. Compared to non-optimally treated elderly patients (PFS 14.9 and OS 24.9 months) the absolute benefit of an optimal treatment in elderly patients was 18.4 months for PFS and 33.8 months for OS (Fig. 1B, $p = 0.002$ and $p < 0.001$, respectively).

3.6. Reasons for early treatment discontinuation in elderly patients

A premature end of the study, as defined as a maximum of 4 cycles of platinum-taxane based chemotherapy, was documented in 18.1% (65/359) of the patients ≥70 years and in 9.2% (275/2974) of the patients <70 years. Patients' refusal and toxicity were named as reasons for early therapy discontinuation in elderly more frequently than younger patients (both $p = 0.001$). In younger and elderly patients favourable ECOG statuses at the time point of registration and the execution of cycle delays were associated with higher rates of therapy completion (both $p = 0.001$). As shown at Table 4A, 33 of 65 elderly patients with early treatment abandonment were treated in the control-arms (TC) and 32 patients were treated in the experimental arms. Among the 72 reasons given for early treatment discontinuation among elderly 32 were related to toxicity and 18 to patients' refusal. In 16 cases progressive disease or patients' death were documented (Table 4B), remarkably with a single peak of patients' deaths at cycle 1. The rate of discontinuation almost levelled over the first 4 courses of chemotherapy with a slight decrease at cycle 3.

3.7. Variations of chemotherapeutic delivery in patients ≥70 years

3.7.1. Dose reductions

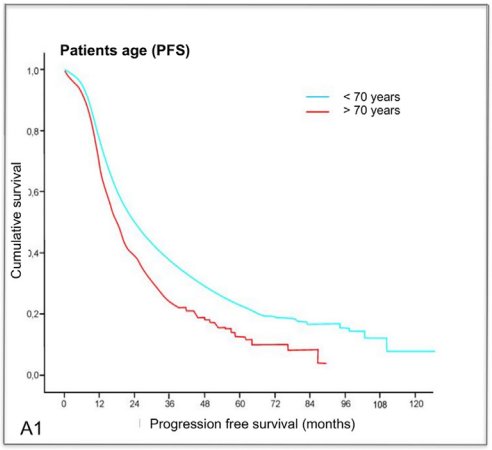
64 (18.1%) of the elderly patients underwent at least one dose reduction. Dose reductions were performed as specified by underlying study protocols due to non-hematologic (n = 33) and hematologic (n = 22) toxicities and allergic reactions (n = 1). In 5 patients dose reductions were performed due to organisational reasons and in 1 patient due to patients' wish. In 2 cases the reason for dose reductions were not further defined. 6 patients underwent a dose reduction first-time at therapy cycle 2, 12 patients at cycle 3, 10 patients at cycle 4, 9 patients at cycle 5 and 27 patients after cycle 5. Dose reductions did neither significantly influence the survival prognoses in this group nor the chance of therapy completion (>4 cycles of chemotherapy) (81% without vs. 86% with at least one dose reduction, $p = 0.354$).

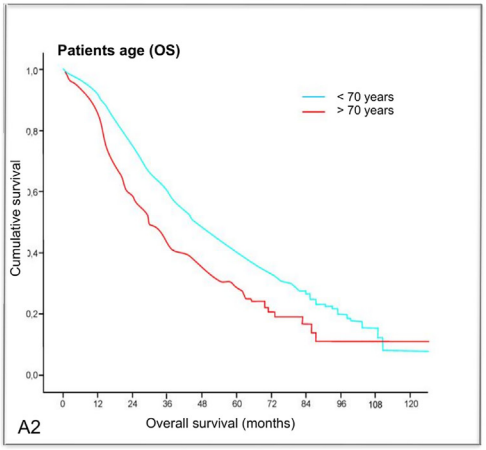
3.7.2. Cycle delays

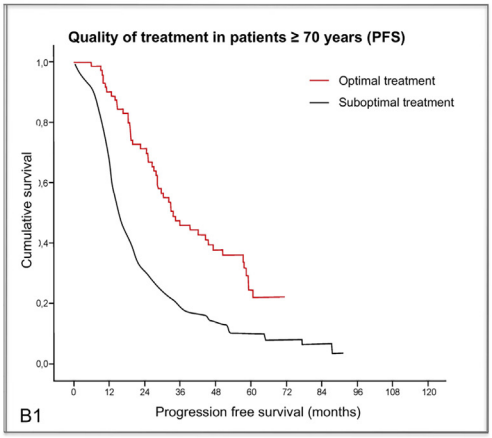
231 (64.3%) of the elderly patients experienced at least one delay of chemotherapy application. Cycle delays were performed as specified by study protocol due to hematologic (n = 49) and non-hematologic (n = 33) toxicities, whereas organisational reasons and patients' wish were documented as the reasons for cycle delays in 141 patients. In 8 patients the reasons for cycle delays were retrospectively inexplicable. 1 elderly patient underwent the first cycle delay at therapy cycle 2, 91 patients at cycle 3, 40 patients at cycle 4 and 99 patients at cycle 5 or later. Cycle delays per se did not significantly influence the survival prognosis (Table 2). 294 of 359 elderly patients were able to complete >4 cycles of chemotherapy. 211 of these 294 patients underwent a total of 450 cycle delays. 204 (45%) cycle delays were performed over the first 4 cycles of chemotherapy. In the group of 65 patients with <5 cycles of the assigned chemotherapy only 20 patients underwent a total of 29 cycle delays. The rate of therapy completion was significantly higher in the group of elderly patients with at least one cycle delay during therapy (91.3% vs. 64.8%, $p < 0.001$).

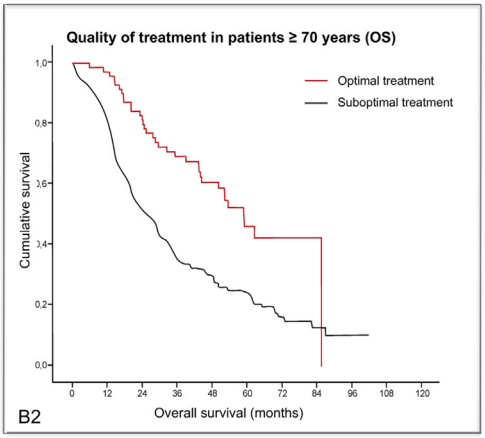
3.8. Age specific differences in the toxicity profile

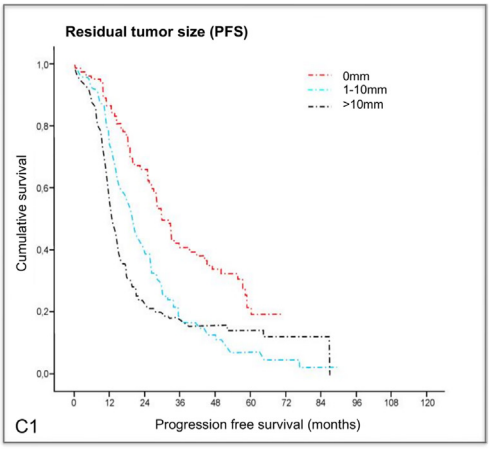
Differences in toxicities between patients of both age groups were evaluated comparing the highest grade of toxicity documented over the course of therapy among the meta-data set of the 3 trials. This pooled analysis was based on the Common Toxicity Criteria data of

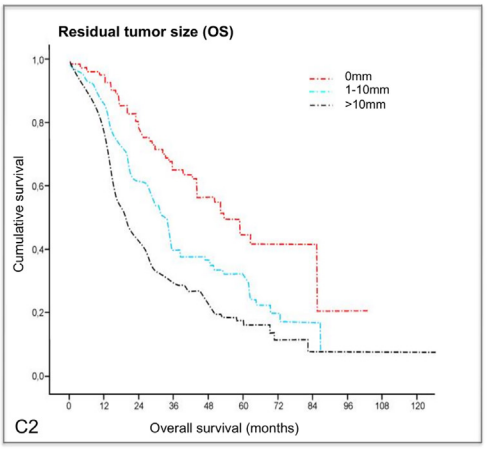

Patients age (PFS)
< 70 years
> 70 years
Cumulative survival
Progression free survival (months)
A1

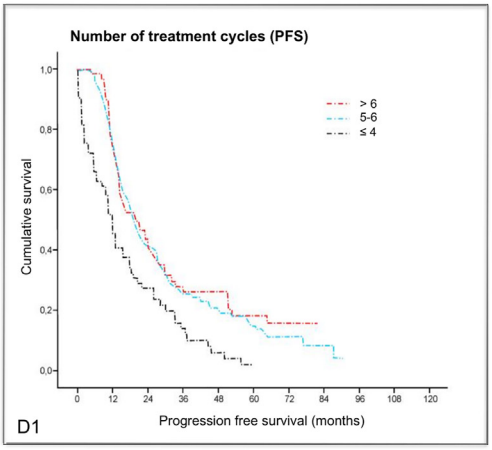

Patients age (OS)
< 70 years
> 70 years
Cumulative survival
Overall survival (months)
A2


Quality of treatment in patients ≥ 70 years (PFS)
Optimal treatment
Suboptimal treatment
Cumulative survival
Progression free survival (months)
B1


Quality of treatment in patients ≥ 70 years (OS)
Optimal treatment
Suboptimal treatment
Cumulative survival
Overall survival (months)
B2


Residual tumor size (PFS)
0mm
1-10mm
>10mm
Cumulative survival
Progression free survival (months)
C1


Residual tumor size (OS)
0mm
1-10mm
>10mm
Cumulative survival
Overall survival (months)
C2


Number of treatment cycles (PFS)
> 6
5-6
≤ 4
Cumulative survival
Progression free survival (months)
D1

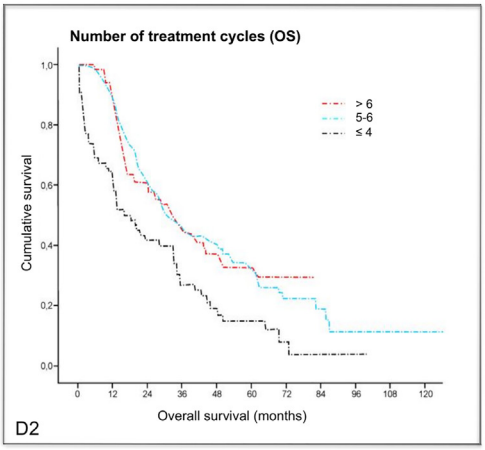

Number of treatment cycles (OS)
> 6
5-6
≤ 4
Cumulative survival
Overall survival (months)
D2

Table 2
Univariate survival analyses of 359 patients ≥70 years with treatment characteristics and therapy modifications. p-Values < 0.05 were considered significant.

Patient and therapy characteristics		Progression free survival			Overall survival		
		Median (months)	95% CI	p-Value	Median (months)	95% CI	p-Value
Performance status	ECOG 0–1	18.4	15.8–20.9	0.863	29.8	25.9–33.6	0.755
	ECOG 2	17.9	12.7–22.9		28.7	10.7–46.8	
Body mass index	<19	12.4	8.2–16.7		17.5	6.1–28.9	
	19–24	17.6	14.9–21.0	0.123	29.5	25.0–34.0	0.189
	>24	18.3	15.6–24.6		33.2	27.9–38.6	
FIGO stage	IIB–IIIB	25.9	12.1–39.7	<0.001	53.1	37.8–68.4	<0.001
	IIIC–IV	16.6	14.1–19.0		26.6	22.2–31.1	
Histologic subtypes	Serous papillary	18.4	13.4–15.8		29.8	25.1–34.4	
	Endometrioid	14.6	16.2–20.5	<0.001	29.6	10.1–49.1	<0.001
	Mucinous	8.3	7.0–9.5		9.3	7.1–11.5	
Postoperative tumor burden	0 mm	30.2	25.5–34.9		53.4	42.5–64.3	
	1–10 mm	20.0	17.0–23.0	<0.001	33.8	29.4–38.2	<0.001
	>10 mm	13.1	11.8–14.4		19.7	15.3–24.1	
Number of treatment cycles	≤4 cycles	11.9	9.4–14.3		18.4	10.4–26.5	
	5–6 cycles	19.3	17.1–21.5	<0.001	30.9	26.5–35.3	<0.001
	>6 cycles	19.6	12.1–27.1		32.5	22.4–42.6	
Dose reductions	Yes	23.9	15.3–19.9	0.218	36.1	23.0–49.2	0.112
	No	17.6	16.4–31.4		29.0	23.5–34.5	
Cycle delays	Yes	18.3	15.9–20.8	0.786	30.2	25.0–35.4	0.368
	No	17.9	13.6–22.1		29.0	21.6–36.3	

patients receiving either Carboplatin/Taxol (TC), Carboplatin/Taxol → Topotecan (TCTop), Carboplatin/Taxol/Epirubicin (TEC) or Cisplatin/Taxol (PT) (Table 5). No significant differences between both age groups were found with regard to hematologic toxicities. Higher rates of grade 1–4 arrhythmia and cardiovascular toxicity as well as grade 3–4 cranial neuropathy were found among elderly patients, whereas less grade 3–4 pain, grade 1–4 myalgia, grade 1–2 alopecia and mucositis were documented among elderly. In the subgroup of elderly patients assigned the TC-control arms age-specific disadvantages only remained for grade 1–4 arrhythmia. Again, less grade 1–2 alopecia and mucositis was observed (Table 5).

3.9. Treatment limiting toxicities in elderly patients

Documented toxicities of elderly patients with early treatment discontinuation were separately analysed and compared to elderly patients with >4 cycles of chemotherapy. Patients with early abandonment of treatment suffered at least twice as often from grade 3 and 4 anaemia, leukopenia and thrombocytopenia at their last treatment cycle. As most common non-hematologic grade 3 and 4 toxicities infections, pain, dyspnoea and diarrhea were named in this context, each of which was at least five times more common compared to the patients with therapy completion. Also, in patients with early treatment discontinuation due to their own wish dyspnoea, febrile neutropenia and infections as well as sensory neuropathy were reported as toxicities in >20% and therefore exceed their frequency in the reference group of elderly patients.

All documented toxicities in elderly patients over the first 4 cycles of therapy are summarized at Supplementary Table 2.

4. Discussion

The medical need for an optimization of treatment strategies in elderly OC patients persists. General frailty, pronounced comorbidities and polypharmacies with possible drug interactions are suspected to counteract the elderly patients' tolerance towards standard surgical and chemotherapeutic interventions or study enrolments. With a participation rate of only about 10% of patients aged ≥70 years we found a distinct underrepresentation of elderly patients in the 3 phase III trials that generated our meta-data set [11–13]. This underrepresentation in clinical trials is a well-known and repeatedly discussed problem also for other tumor entities, which might consequence misinterpretations of clinical findings, as results of phase III trials may establish therapeutic standards, which might be inadequate for this neglected patient group [14,15]. Therefore, more age-specific, even prospective, clinical trials were initiated over the last couple of years [16,17].

Several studies focussed on the topic of non-enrolment of possibly eligible aged OC patients and it is hypothesized that more functional and social aspects need to be considered, such as a possible lack of social support and an additional effort of time and resources upon study enrolment [18,19]. The 5th Ovarian Cancer Consensus Conference of the Gynecological Cancer Intergroup in 2015 stated that older age per se should not be an exclusion criterion in ovarian cancer trials and any limitations to eligibility criteria based on performance status, comorbidities and prior malignancies should be justified by the trial design. Once enrolled, also in our analysis an underlying study participation bias has to be assumed possibly leading to an evaluation of mainly "fit" elderly patients who met the inclusion criteria and convinced investigators. Counterintuitively, the ECOG performance status upon initial presentation could not be validated as an independent prognostic marker for elderly patients in our study collective (ECOG 0–1 vs. 2; Tables 2 and 3). This parameter has been repeatedly criticized due to a limitation in its prognostic validity and an increasing reservation concerning the use of ECOG performance status for elderly patients in clinical trial settings can be observed. Moreover, multidimensional evaluations in terms of comprehensive geriatric assessments are used particularly in age-specific designed trials, in which clinical, mental, nutritive and social aspects of the aged patients are incorporated and evaluated to enable an individualized, age-adjusted treatment application for an optimal therapeutic success [20–23].

In our study, we were able to show a marked clinical benefit of 18.4 months in PFS and 33.8 months OS in the group of 71 elderly

Fig. 1. Kaplan-Meier estimates for PFS (1) and OS (2) depending on patients age (A) and in elderly patients with and without optimal treatment (defined as no residual tumor burden and at least 5 cycles of a platinum- and taxane- based chemotherapy) (B). Kaplan-Meier estimates for the residual tumor burden after cytoreductive surgery (C) and for the number of delivered chemotherapeutic treatment cycles (D) for elderly patients are shown. Levels of significance are depicted at Table 3.

Table 3
Multivariate survival analyses of patients characteristics and treatment variables over the course of therapy on PFS and OS in 359 patients ≥70 years. p-Values < 0.05 were considered significant.

Parameters		Progression free survival			Overall survival		
		Hazard ratio	95% CI	p-Value	Hazard ratio	95% CI	p-Value
Performance status	0–1 vs. 2	0.781	0.543–1.123	0.182	0.799	0.532–1.200	0.279
Body mass index	<19 vs. 19–24	1.309	0.819–2.093	0,26	1.671	1.021–2.735	0.041
	>24 vs. 19–24	0.800	0.608–1.053	0.112	0.983	0.726–1.332	0.983
FIGO stage	IIIC–IV vs. IIB–IIIB	1.731	1.271–2.462	0.002	1.978	1.345–2.907	<0.001
Histologic subtypes	Endometrioid vs serous	1.504	0.922–2.454	0.102	1.412	0.843–2.366	0.190
	Mucinous vs serous	3.304	1.920–5.686	<0.001	5.435	3.115–9.484	<0.001
Postoperative tumor burden	0 vs. 1–10mm	0.578	0.401–0.832	0.003	0.597	0.395–0.901	0.001
	>10 vs. 1–10mm	1.280	0.955–1.717	0.099	1.405	1.030–1.917	0.032
Number of treatment cycles	≤4 vs. 5–6	2.257	1.556–3.274	<0.001	2.078	1.402–3.082	<0.001
	>6 vs. 5–6	0.790	0.570–1.093	0.154	0.975	0.681–1.395	0.889
Dose reductions	Yes vs. No	0.820	0.585–1.147	0.246	0.741	0.504–1,090	0.128
Cycle delays	No vs. Yes	1.286	0.964–1.715	0,87	1.080	0.797–1.463	0.620

patients upon an optimal therapy, which was defined as no residual tumor burden after upfront surgery and >4 cycles of platinum/taxane-based chemotherapy. But detailed analyses of the chemotherapeutic delivery showed an early treatment discontinuation in 65 of 359 elderly patients, which is of special interest as the application of >4 cycles of chemotherapy alone led to a survival benefit of 12 months (Table 2). 16 elderly patients suffered from either progressive disease or death within the first 4 treatment cycles, interestingly 11 of them already within the first 2 cycles. We assume that these courses of therapy are more likely to be explained by perioperative complications and higher tumor residua than by chemotherapy-induced complications. Over the first 4 cycles of chemotherapy the rates of treatment abandonment then almost levelled with a noticeable decrease at cycle 3 (Table 4B), which might be explained by higher rates of cycle delays and dose reductions at this time point. Toxicities, followed by patients' refusal and progressive disease, were the main reasons for a treatment discontinuation. No differences in treatment abandonment rates were observed between the control and experimental treatment arms (18.5% vs. 17.6% of elderly patients, Table 4A). With a special emphasis on possible age specific toxicities (as defined by NCI Common Toxicity Criteria) we compared toxicity profiles of elderly patients and younger patients over the course of therapy. Whereas lower total numbers of applied therapy cycles among elderly patients have to be kept in mind, we found just 3 of 23 examined highest grade toxicity items (arrhythmia, cardiovascular toxicity and cranial neuropathy) to significantly differ between the age groups to the disadvantage of elderly patients in our total collective. When exclusively patients assigned to the Carboplatin/Taxol-arms were considered only arrhythmia persisted to adversely affect elderly patients in particular (Table 5). In terms of toxicity management, hematologic toxicities as febrile neutropenia and infections, which were named as prominent toxicities leading to treatment abandonment by patients ≥70 years, might have exemplarily been attenuated by a more consequent prescription of G-CSF, which was permitted in all study protocols. Also remarkably, in >50% of patients ≥70 years with early treatment discontinuation due to their own wish gastrointestinal complications (nausea, vomiting, constipation) were documented. We found the stringent use of antiemetic medication to be significantly associated with higher rates of therapy completion in elderly patients. In line with these hypotheses, we observed a survival benefit of 7 months when at least one dose reduction was performed (HR 0.741, p = 0.128, not significant). It already has been proposed that dose reductions might improve elderly patients' tolerance to platinum/taxane-based therapies without reducing the therapy effectiveness [24]. Another phase II study proposed a weekly schedule of a platinum- and paclitaxel-based chemotherapy to further minimize toxicities in this context [25]. Hilpert et al already addressed this question of toxicity in elderly OC patients and found that the application of a platinum- and paclitaxel-based chemotherapy is feasible in patients ≥70 years without a specific impairment of the quality of life compared to younger patients [6]. Even the clinically relevant additive use of Bevacizumab or the PARP-inhibitor Olaparib does not seem to disadvantage elderly patients as long as possible restraints like baseline arterial hypertension are carefully considered [26,27]. Additionally, the main reasons for cycle delays, which in turn led to higher therapy completion rates in our collective, were rather organisational efforts and patients' wish than toxicities. Strikingly, in the group of the elderly patients with therapy completion 72% of the patients underwent at least one cycle delay during chemotherapeutic treatment, whereas cycles delays were observed in only 31% of the patients with early treatment discontinuation. We therefore assume that a more liberal management of protocol violations by exploiting predefined rules for dose reductions and cycle delays might lead to higher rates of therapy completion in elderly patients.

Table 4
A. Number of applied chemotherapy cycles of study patients divided by treatment arms (TC: paclitaxel-carboplatin; TCTop: paclitaxel-carboplatin → topotecan; TEC: paclitaxel-carboplatin plus epirubicin; TP: paclitaxel-cisplatin).
B. Reasons for early treatment discontinuation (≤4 cycles of platinum/taxane-based chemotherapy) divided by occurrence during the first 4 cycles in a total of 65 patients ≥70 years. Multiple answers possible.

A					
		Number of applied cycles			
		≤4	5–6	>6	*Total*
TC	<70 years	121	1167	196	*1484*
	≥70 years	**33**	131	14	*178*
	Total	*154*	*1298*	*210*	*1662*
TCTop	<70 years	57	56	464	*577*
	≥70 years	**11**	9	53	*73*
	Total	*68*	*65*	*517*	*650*
TEC	<70 years	59	447	63	*569*
	≥70 years	**10**	55	3	*68*
	Total	*69*	*502*	*66*	*637*
TP	<70 years	38	288	18	*344*
	≥70 years	**11**	29	0	*40*
	Total	*49*	*317*	*18*	*384*
Pooled analysis	<70 years	275	1958	741	2974
	≥70 years	**65**	224	70	359
	Total	*340*	*2182*	*811*	***3333***

B					
≥70 years reasons	**Cycle 1** n=22pts	**Cycle 2** n=17pts	**Cycle 3** n=9pts	**Cycle 4** n=17pts	**Total n=65pts**
Toxicity	**8**	**10**	**5**	**9**	**32**
Patients choice	**6**	**2**	**5**	**5**	**18**
Physicians choice	–	1	–	–	1
Protocol violation	–	1	–	–	1
Others	2	1	–	1	4
Total	*16*	*15*	*10*	*15*	*56*
Progress of disease	1	3	1	2	7
Death	5	2	1	1	9
Total	*22*	*20*	*12*	*18*	*72*

Table 5
Comparison of highest-grade toxicities over the course of therapy divided by age groups, toxicity grade according to NCI Common Toxicity Criteria and treatment arms:
TC: paclitaxel-carboplatin.
TCTop: paclitaxel-carboplatin → topotecan.
TEC: paclitaxel-carboplatin plus epirubicin.
TP: paclitaxel-cisplatin.

		Pooled analysis: TC, TCTop, TEC, TP					Analysis of solely TC-arms from 3 studies					
Toxicity grade		**0**	**1–2**	**3–4**	***Total***	**p-Value**	**0**	**1–2**	**3–4**	***Total***	**p-Value**	*
Anaemia	<70 years	217	2362	301	*2880*	0.059	137	1213	87	*1437*	0.385	TEC
	≥70 years	**22**	**271**	**50**	***343***		**11**	**148**	**12**	***171***		
Neutropenia	<70 years	561	597	1485	*2643*	0.583	280	367	666	*1313*	0.841	
	≥70 years	**61**	**64**	**182**	***307***		**35**	**40**	**75**	***150***		
Febrile Neutropenia	<70 years	2604		94	*2698*	0.052	1317		25	*1342*	0.257	
	≥70 years	**300**		**18**	***318***		**151**		**5**	***156***		
Thrombo-cytopenia	<70 years	1309	1225	345	*2879*	0.554	733	604	99	*1436*	0.941	
	≥70 years	**151**	**144**	**48**	***343***		**87**	**71**	**13**	***171***		
Infections	<70 years	1866	722	13	*2701*	0.088	987	322	34	*1343*	0.219	
	≥70 years	**214**	**84**	**22**	***320***		**118**	**31**	**7**	***156***		
Diarrhea	<70 years	1933	681	86	*2700*	0.826	1000	302	40	*1342*	0.301	
	≥70 years	**235**	**76**	**10**	***321***		**110**	**43**	**3**	***156***		
Nausea	<70 years	608	1932	166	*2706*	0.320	379	909	57	*1345*	0.575	
	≥70 years	**83**	**222**	**16**	***321***		**50**	**99**	**7**	***156***		
Vomiting	<70 years	1426	1156	120	*2702*	0.700	778	527	37	*1342*	0.829	
	≥70 years	**171**	**139**	**11**	***321***		**91**	**62**	**3**	***156***		
Arrhythmia	<70 years	2396	274	33	*2703*	0.000	1201	130	13	*1344*	0.008	TCTop, TEC
	≥70 years	**257**	**51**	**13**	***321***		**127**	**25**	**4**	***156***		
Cardiovas-cular toxicity	<70 years	1947	55	5	*2007*	0.019	965	27	5	*997*	0.660	TCTop, TEC
	≥70 years	**224**	**10**	**3**	***237***		**108**	**4**	**0**	***112***		
Creatinine increase	<70 years	2684	204	10	*2898*	0.205	1368	71	6	*1445*	0.370	TP
	≥70 years	**314**	**33**	**2**	***349***		**161**	**10**	**2**	***173***		
Edemata	<70 years	2140	545	19	*2704*	0.353	1092	241	11	*1344*	0.490	
	≥70 years	**243**	**75**	**3**	***321***		**121**	**34**	**1**	***156***		
Constipation	<70 years	1345	1034	319	*2698*	0.490	696	507	138	*1341*	0.233	TP
	≥70 years	**149**	**133**	**39**	***321***		**76**	**57**	**23**	***156***		
Cranial Neuropathy	<70 years	2152	514	34	*2700*	0.009	1088	239	16	*1343*	0.090	
	≥70 years	**253**	**56**	**11**	***320***		**127**	**23**	**5**	***155***		
Sensory Neuropathy	<70 years	801	1751	148	*2700*	0.059	404	877	62	*1343*	0.068	
	≥70 years	**94**	**198**	**28**	***320***		**55**	**89**	**12**	***156***		
Pain	<70 years	1141	1291	267	*2699*	0.008	590	611	142	*1343*	0.097	
	≥70 years	**150**	**156**	**15**	***321***		**71**	**77**	**8**	***156***		
Myalgia	<70 years	1186	1394	119	*2699*	0.007	595	685	62	*1342*	0.100	
	≥70 years	**170**	**142**	**9**	***321***		**83**	**68**	**5**	***156***		
Allergy	<70 years	2267	369	81	*2717*	0.216	1127	190	34	*1351*	0.999	
	≥70 years	**280**	**34**	**7**	***321***		**130**	**22**	**4**	***156***		
Dyspnea	<70 years	2025	549	130	*2704*	0.180	1017	266	61	*1344*	0.675	TEC
	≥70 years	**228**	**71**	**22**	***321***		**113**	**35**	**8**	***156***		
Alopecia	<70 years	107	2592		*2699*	0.000	52	1293		*1345*	0.000	
	≥70 years	**31**	**290**		***321***		**18**	**138**		***156***		
Mucositis	<70 years	2010	672	18	*2700*	0.003	1055	282	5	*1342*	0.024	TEC
	≥70 years	**261**	**55**	**5**	***321***		**137**	**19**	**0**	***156***		
Stomatitis	<70 years	573	113	2	*688*	0.348	289	54	1	*344*	0.476	
	≥70 years	**75**	**9**	**0**	***84***		**40**	**4**	**0**	***44***		
Hearing defects	<70 years	2454	229	17	*2700*	0.442	1229	108	6	*1343*	0.863	
	≥70 years	**288**	**28**	**4**	***320***		**144**	**11**	**1**	***156***		

* indicates significant age-specific differences in the respective experimental arms.
p-Values < 0.05 were considered significant.

Falandry et al published a trial in an even more morbid cohort of aged OC patients [17]. Prospectively addressing the question of vulnerability in 111 elderly patients upon first-line chemotherapy with carboplatin this group found profoundly more grade 3–4 hematologic toxicities in their cohort, while, in a comparable dimension to our data, about 75% of the patients were able to complete their therapy. As

a consequence a geriatric vulnerability score (GVS) was established to identify 2 groups of elderly patients with different prognoses as well as chances of therapy completion and therapy-associated complications. This score was just recently validated in a pooled analysis of 3 phase-II-trials. Here the authors found an increased HADS-Score (Hospital Anxiety and Depression Scale) and a decreased IADL-Score (Instrumental Activities of Daily Living) to negatively impact the OS in their elderly patients' cohort whereas the toxicities upon chemotherapeutic treatment were stated to be manageable [28]. Currently, this GVS is being prospectively tested in a phase III trial of patients >70 years of age (EWOC-1, NCT02001272). Interestingly, the IADL-Score was recently shown to be associated with a chance of completion of 4 cycles of platinum- or platinum/taxane-based chemotherapies regardless of dose reductions or cycle delays among OC patients >70 years of age [29].

The exploration of neoadjuvant chemotherapy (NACT) strategies in OC patients also gained special interest in terms of reduction of therapy-associated complications. Two phase 3 trials proved no-OS-inferiority of interval debulking surgery after neoadjuvant platinum/taxane based chemotherapy compared to upfront cytoreductive surgery in advanced OC stages, even with a survival benefit in stage IV disease [30]. No differences between quality of life were found between both treatment regimens [31]. In this context, guidelines of the American Society of Gynecologic Oncology recommend upfront surgery in advanced OC (IIIC-IV) patients "if there is a high likelihood of achieving cytoreduction to <1 cm (ideally to no visible disease) with acceptable morbidity" [32]. In our collective a postoperative tumor of <1 cm was achieved in 53% of the patients ≥70 years. Meyer et al recently performed an analysis of the use and effectiveness of the increasing application of NACT especially in elderly (≥66 years) OC patients [33]. Whereas higher rates of treatment related complications (colostomies, ER visits, readmissions) were observed in the group of elderly patients receiving upfront surgery (23.3% vs. 10.8%), the median OS was significantly longer compared to NACT (38.8 vs. 28.0 months). Furthermore, no survival benefit for either treatment plan was observed for elderly patients with stage IV disease. Another single institution analysis also found less surgical and chemotherapeutic complications in elderly OC patients receiving NACT, without survival benefit in either treatment strategy [34]. Therefore, the indication of upfront surgery or NACT with interval surgery should incorporate a more diversified approach than just patients' age. NACT should be considered as an appropriate therapy alternative in elderly patients with unlikely tumor resectability or high perioperative risks.

Taken together, our data provide a rationale for the completion of surgical and especially chemotherapeutical treatment standards in fit elderly OC patients. A comprehensive geriatric assessment, a more personalized approach and an overcoming of physicians' unfounded concerns might help to identify elderly patients, who might be then offered standard oncologic treatments or even study enrolment. The consequent use of complementary medicine might reduce individual discomforts and medical complications and therefore support patients' treatment adherence. The present data should encourage investigators and elderly patients to accomplish oncologic treatment standards with utilization of given study protocol defined instruments like dose reductions or cycle delays to avoid unnecessary toxicities.

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Conflict of interest

The authors declare no conflict of interest.

Ethics approval

The study was performed in accordance with the Declaration of Helsinki.

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Availability of data and materials

Study protocols and patients' data were retrieved from the AGO Studiengruppe, AGO Research GmbH, Kaiser-Friedrich-Ring 71, 65185 Wiesbaden, Germany.

Authorship

T.H. participated in data analyses and wrote the manuscript. A.H. and S.S. generated the data as a part of their doctoral theses. J.H. supported the statistical computation. J.P., E.P.-L., P.H. and A.dB. made substantial contributions to the underlying phase III trials and participated in drafting and reviewing of the manuscript. F.H. designed the underlying analyses and interpreted the data.

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