Comprehensive geriatric assessment predicts tolerance to chemotherapy and survival in elderly patients with advanced ovarian carcinoma: a GINECO study


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Background: Data from prospective clinical trials are needed to better define standards of care in elderly patients with advanced ovarian carcinoma and to demonstrate the interest of Comprehensive Geriatric Assessment (CGA) in this fragile and heterogeneous population.

Patients and methods: From July 1998 to October 2000, 83 advanced ovarian carcinoma patients >70 years old received carboplatin AUC 5 and cyclophosphamide 600 mg/m², on day 1 of six 28-day cycles. The clinical and biological geriatric covariates prospectively studied were: comorbidities, medications, cognitive functions (Mini-Mental test), nutritional status and autonomy.

Results: Patient characteristics were: median age 76 years, serous histology (73%), FIGO stage III (75%), optimal initial surgery (21%) and performance status (PS) ≥2 (44%). Sixty patients (72%) received six chemotherapy cycles without severe toxicity (STox) or tumor progression. Multivariate analysis retained three factors as independent predictors of STox: symptoms of depression at baseline (P = 0.006), dependence (P = 0.048) and PS ≥2 (P = 0.026). Independent prognostic factors identified for overall survival (Cox model) were depression (P = 0.003), FIGO stage IV (P = 0.007) and more than six different medications per day (P = 0.043).

Conclusion: CGA could predict STox and overall survival of elderly advanced ovarian carcinoma patients.

Key words: chemotherapy, elderly, geriatric assessment, ovarian cancer

Introduction

Ovarian cancer frequently occurs in women >70 years old and its incidence is maximal in the seventh to eighth decades of life [1]. A large international study showed that elderly patients have lower survival rates, despite treatment, and that older age is an independent predictor of poor prognosis [2]. Several factors have been proposed to explain this difference between elderly women and their younger counterparts: more advanced stage at diagnosis, lower percentage with optimal debulking and non-optimal chemotherapy for fear of severe toxicity (STox). However, the results of numerous studies on various tumor types suggest that chemotherapy is feasible and effective in patients >70 years old [3–5], but most of these studies were conducted on selected subgroups of elderly patients included in controlled trials [4]. In routine practice, the main characteristic of the population of elderly patients is heterogeneity: some will tolerate chemotherapy as well as younger women, others will experience unpredictable and STox, mainly hematological side-effects [6]. A possible way to overcome this variability and therefore to identify the patients at risk of STox is to use specific tools developed by geriatricians and included in the so-called Comprehensive Geriatric Assessment (CGA). A recent study showed that CGA adds useful information to the evaluation of WHO-ECOG performance status (PS) alone in patients with cancer [7], but the possibility that CGA parameters might be able to predict efficacy and tolerance of chemotherapy needs to be evaluated prospectively [8].

The aim of this study, specifically performed in elderly patients with stage III/IV ovarian carcinoma, was to evaluate the ability of some CGA parameters to predict efficacy and...
tolerance of the carboplatin + cyclophosphamide combination, in order to identify which subgroups of elderly patients should receive standard or dose-reduced therapy and for whom chemotherapy would not be beneficial.

Patients and methods

Type of study

The study was an open multicenter prospective study to identify prognostic factors. Its protocol was approved by the Lyon University Hospital Independent Ethics Committee in June 1998. The primary objectives of this study were to evaluate patients tolerance of a combined carboplatin + cyclophosphamide regimen (see Treatment), with calculation of the percentage completing six 28-day cycles, and the relevance of CGA parameters to predict the probability of STox (see below). Secondary objectives included assessment of chemotherapy-induced side-effects, and progression-free and overall survival.

Patients

We included patients >70 years old with stage III or IV ovarian epithelial carcinoma, who met the following criteria: cytologically or histologically proven epithelial carcinoma, initial laparotomy or not, normal blood counts with neutrophils >1.5 g/l and platelets >100 g/l, no prior irradiation, and absence of icterus. A patient was eligible, regardless of PS (ECOG), if her treating physician considered that she could receive chemotherapy.

Pre-treatment screening

Screening before inclusion in the study comprised: PS evaluation, complete blood counts, hemoglobin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyl transferase, blood electrolytes, serum creatinine and urea, CA-125 assay, biological nutritional status (see Comprehensive Geriatric Assessment), electrocardiogram, and computed tomography (CT) scans of the chest, abdomen and pelvis.

Treatment

Patients were scheduled to receive carboplatin AUC 5 according to the Chatelut formula + cyclophosphamide 600 mg/m² every 28 days for six cycles. Carboplatin and cyclophosphamide were given during successive 30-min infusions. Antiemetics were given intravenously: ondansetron 8 mg or granisteron 3 mg + methylprednisolone 1 mg/kg. An intermediate laparotomy after three cycles was not planned.

Dose reductions were planned as follows: for grade 4 neutropenia lasting >7 days, febrile neutropenia, grade 4 thrombocytopenia, incomplete hematological recovery on day 35 (neutrophils <1.5 g/l, platelets <100 g/l) or grade 2 neurotoxicity, the carboplatin dose was reduced to AUC 4 and the cyclophosphamide dose to 500 mg/m² for all subsequent cycles. If toxicity persisted despite dose reduction, chemotherapy was considered unfeasible.

Treatment feasibility was defined as the patient’s ability to receive six courses of this chemotherapy regimen without disease progression, death due to any cause, patient’s or investigator’s decision to stop treatment, persistent toxicity as defined above despite dose reduction, or any grade 3/4 non-hematological toxicity.

Comprehensive Geriatric Assessment

During the consultation immediately preceding inclusion and first chemotherapy cycle, each patient completed with the investigator the CGA evaluation. Patient autonomy was assessed according the following categories: full autonomy at home or dependence (living at home with assistance, living with medical assistance in a specialized institution). We also recorded all comorbidities, mainly heart and vascular diseases, respiratory disease, diabetes, liver and kidney function test results, and the number of different drugs taken daily at baseline (zero to three, four to six, or more than six).

Nutritional status was assessed by body mass index (BMI), protidemia, albuminemia and total cholesterol. Cognitive function was evaluated with the Mini-Mental Status (MMS) test developed by Folstein et al. [9]. The presence or absence of clinical symptoms of depression was assessed by the investigator.

Evaluation criteria for toxicity and efficacy

Chemotherapy-induced side-effects were assessed at each cycle using the National Cancer Institute Common Toxicity Criteria, version 1. We defined the STox as the occurrence of at least one of the following events: febrile (>38.5°C) neutropenia, grade 4 neutropenia, early treatment withdrawal because of grade 3/4 toxicity or re-hospitalization for >7 days for grade 3/4 toxicity.

For patients with initial measurable tumor masses >2 cm in the largest diameter, tumor response was evaluated by CT scans after three and six cycles of chemotherapy.

Statistical analysis

The number of patients to be included was calculated with the intent to reject the null hypothesis of a <59% rate of chemotherapy feasibility, with α = 10% and β = 5% (unilateral hypothesis). Based on this assumption, 80 patients should be included.

Survival analysis. Overall survival, from inclusion to the patient’s death, and progression-free survival, from study entry until disease progression confirmed clinically, radiologically or biologically (CA-125 increase), were estimated using the Kaplan–Meier method with censored data and compared using the log-rank test.

Predictive STox and prognostic factors. To predict STox and identify prognostic factors, we analyzed the occurrence of chemotherapy-induced STox as defined above. Progression-free and overall survival and CGA parameters were subjected to univariate analyses using the Pearson χ²-test and Fisher’s exact tests for categorical variables, and the non-parametric Mann–Whitney U-test for continuous variables. The following covariates were assessed at baseline: (i) chronological age; (ii) PS; (iii) MMS: (iv) autonomy; (v) comorbidities; (vi) number of daily comedication; (vii) nutritional status; (viii) hematomal, renal and liver function parameters; (ix) tumor characteristics: FIGO stage (III versus IV), histology (serous subtype versus others), optimal initial surgery with residual tumor masses <1 cm (versus non-optimal surgery), absence (versus presence) of ascites or pleural effusion, involvement of liver or lung (versus no involvement), number of involved sites, and CA-125 level.

A logistic regression model was constructed by stepwise introduction of covariates that had been significantly associated with STox criteria (P < 0.05), according to our univariate analysis.

To identify the prognostic factors of progression-free and overall survival, a Cox model was used in which significant covariates coming from the univariate analysis (P < 0.05), were introduced stepwise to obtain the final model.

All tests were two-sided. Analyses were performed using the SPSS® version 10.0 statistical package (SPSS Inc., Chicago, IL, USA).

Results

Patients characteristics

From July 1998 to October 2000, 83 patients >70 years old with advanced ovarian carcinoma were enrolled in 30 centers. Their
characteristics are summarized in Table 1. Ninety per cent of them had undergone an initial laparotomy with or without tumor debulking. For the remaining 10%, a pelvic mass had been found at CT scan, CA-125 was above the normal value and the diagnosis was made by cytological examination of pleural or peritoneal effusion.

Comprehensive Geriatric Assessment

CGA comorbidities, comedications and autonomy findings are given in Table 2. The median BMI was 22.89 (SD 4.05). The median total protidemia and albuminemia were 64 g/l (SD 8.08) and 31.3 g/l (SD 12.46), respectively. The median MMS score was 27 (SD 6.41).

Chemotherapy tolerance

A total of 472 chemotherapy cycles were administered. Sixty out of the 83 patients [72%; 95% confidence interval (CI) 64.5% to 80.2%] completed treatment without STox or tumor progression.

The toxicities observed are reported in Table 3 as the percentages of patients affected. Concerning hematological toxicities, grade 3/4 neutropenia, anemia and thrombocytopenia were observed in 28.7%, 9% and 8.3% of the cycles, respectively.

We found no statistically significant predictive factor for grade 3/4 thrombocytopenia, which was observed in 39.5% of patients.

Twenty-three patients (27.7%; 95% CI 19.9% to 39.3%) experienced STox: six developed febrile neutropenia, six discontinued treatment because of hematological toxicity, one grade 3 mucositis, one grade 3 asthenia, one death consecutive to cranial trauma, and hospitalization lasting >7 days for one patient with hematological toxicity, four patients with grade 3 infection, one with grade 4 infection, one with femoral trauma and one with thrombophlebitis. According to our univariate analysis, the covariates reaching statistical significance were: PS ≥2 (P = 0.007), dependence (P = 0.017) and symptoms of depression at baseline (P = 0.006). FIGO stage IV tended towards significance (P = 0.075).

The multivariate analysis retained the following independent factors as predictive of STox: depression (P = 0.006), PS ≥2 (P = 0.026) and dependance (P = 0.048).

Efficacy

Data on CA-125 evolution during chemotherapy were available for 64% of patients. The CA-125 level normalized in 31.4% and decreased <50% in the remaining 24.4%. The radiological tumor response rate, assessable in 48 patients with initial measurable masses, was 48%. Fourteen patients underwent a second-look laparotomy: one histological complete response, three macroscopic complete responses with persistent of

Table 1. Patients characteristics (n = 83)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>median 76, range 70–90</td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>16 (19)</td>
</tr>
<tr>
<td>1</td>
<td>31 (37)</td>
</tr>
<tr>
<td>≥2</td>
<td>36 (44)</td>
</tr>
<tr>
<td>Ascites</td>
<td>49 (59)</td>
</tr>
<tr>
<td>Diagnostic procedure</td>
<td></td>
</tr>
<tr>
<td>Laparotomy</td>
<td>75 (90)</td>
</tr>
<tr>
<td>Pleural or ascites effusion cytology</td>
<td>8 (10)</td>
</tr>
<tr>
<td>FIGO initial stage</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>62 (75)</td>
</tr>
<tr>
<td>IV</td>
<td>21 (25)</td>
</tr>
<tr>
<td>Optimal initial surgery (size of residual lesions)</td>
<td></td>
</tr>
<tr>
<td>&lt;1 cm</td>
<td>16 (21)</td>
</tr>
<tr>
<td>≥1 cm</td>
<td>59 (79)</td>
</tr>
<tr>
<td>Histological subtype</td>
<td></td>
</tr>
<tr>
<td>Serous papillary</td>
<td>61 (73)</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>18 (22)</td>
</tr>
<tr>
<td>Histological grade</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9 (11)</td>
</tr>
<tr>
<td>2</td>
<td>19 (23)</td>
</tr>
<tr>
<td>3</td>
<td>18 (21)</td>
</tr>
<tr>
<td>Unknown</td>
<td>37 (45)</td>
</tr>
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</table>

Table 2. Comprehensive geriatric assessment (n = 83): comorbidities, comedications and autonomy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure (treated)</td>
<td>20 (24.1)</td>
</tr>
<tr>
<td>Vascular disease unrelated to the tumor</td>
<td>19 (22.9)</td>
</tr>
<tr>
<td>Symptoms of depression at study entry</td>
<td>19 (22.9)</td>
</tr>
<tr>
<td>Hypertension (treated)</td>
<td>19 (22.9)</td>
</tr>
<tr>
<td>Chronic respiratory disease</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diabetes type I</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diabetes type II</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Comedications/day</td>
<td></td>
</tr>
<tr>
<td>0–3 drugs</td>
<td>48 (59)</td>
</tr>
<tr>
<td>4–6 drugs</td>
<td>28 (33)</td>
</tr>
<tr>
<td>&gt;6 drugs</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Autonomy</td>
<td></td>
</tr>
<tr>
<td>Complete autonomy at home</td>
<td>61 (73.5)</td>
</tr>
<tr>
<td>Living at home with assistance</td>
<td>13 (15.7)</td>
</tr>
<tr>
<td>Living in a medicalized nursing home</td>
<td>9 (10.8)</td>
</tr>
</tbody>
</table>
histological involvement and six partial responses with macroscopic residual disease were observed.

**Survival**

Median progression-free survival for the entire population was 9.9 months (95% CI 7.2–12.6) (Figure 1A). The multivariate analysis retained the following independent prognostic factors as being independently associated with poorer progression-free survival: depression \((P < 0.003)\), FIGO stage IV \((P < 0.04)\) and initial non-optimal surgery \((P < 0.008)\).

Median overall survival for the entire population was 21.6 months (95% CI 13.4–29.8) (Figure 1B). The multivariate analysis retained the following prognostic factors as being independently associated with poorer overall survival: depression \((P = 0.003)\), FIGO stage IV \((P = 0.007)\) and more than six different comedication drugs per day \((P = 0.04)\).

Figure 1C shows overall survival curves for patients with zero, one, or two or more poor prognosis factors.

**Discussion**

The incidence of ovarian carcinoma is the highest in women over 70 years of age in Western European countries and the USA. Hence, such patients should represent at least 50% of those included in the major clinical trials, but they accounted for <30% of the women enrolled in the Gynecologic Oncology Group 111 randomized trial, which was the first study to demonstrate the usefulness of paclitaxel in combination with cisplatin \[10\]. It is possible that elderly patients included in prospective studies, even randomized trials, are selected by application of age-restrictive eligibility criteria and the reticence
of some investigators [11]. As a consequence, the results of statistical analyses of subgroups of elderly patients included in prospective studies with various tumor types, which suggested that chemotherapy was as well tolerated as in younger patients, should be interpreted with caution [12–14].

The eligibility criteria for our prospective study, which enrolled 83 elderly patients with advanced ovarian carcinoma, were not restrictive, as we included women with poor PS (3 and 4) to avoid selection bias. However, since there was no systematic registration of non-included patients, our results cannot be generalized to the elderly population. The patients of our study had relatively few geriatric conditions (Table 2) and an average life expectancy of 22 months. Despite the motivation of the study had relatively few geriatric conditions (Table 2) and an average life expectancy of 22 months. Despite the motivation of the investigators, more fragile patients were not included. Such patients, usually living in a geriatric institution, are probably not referred to an oncologist.

In 1998, GINECO decided to use the carboplatin + cyclophosphamide combination because of its reported good tolerance and efficacy [15, 16]. Knowing that the International Collaborative Ovarian Neoplasm group recently described similar efficacies of carboplatin alone versus its combination with paclitaxel [17], we can retrospectively admit that carboplatin alone was a reasonable alternative.

However, in our study population, among which 44% of patients had PS ≥2 and 25% had FIGO stage IV, the carboplatin–cyclophosphamide combination was well tolerated, since 72% of patients received six cycles without STox or disease progression. This is an encouraging observation, which leads us to recommend that this combined regimen be a standard in the population of women over 70 years of age.

Furthermore, we must emphasize that initial surgery had been optimal in only 20% of our patients. This is not surprising, since very similar data have already been reported in epidemiological studies [1]. In our opinion, given the clinical consequences of incomplete initial laparotomy in elderly patients with peritoneal carcinomatosis extending beyond the pelvis, and often ascites, chemotherapy as first-line treatment should always be considered.

Among patients who experienced STox necessitating treatment discontinuation, some variables appear to have predictive value. One factor, PS, is not specific to elderly patients. Indeed, it is a variable that is usually associated with patients’ prognosis and/or treatment tolerance in most studies examining various tumor types. Notably, depression symptoms at baseline and loss of autonomy, variables included in the CGA, were predictive of chemotherapy-induced STox. STox is a composite parameter that takes into account all deleterious clinical events in elderly patients: re-hospitalization for STox lasting >7 days, febrile neutropenia and early treatment withdrawal because of toxicity. This parameter must be distinguished from chemotherapy feasibility, which also includes absence of tumor progression and thus could not be included in the predictive analysis.

Symptomatic depression assessment was evaluated by the investigator, who did not use any specific scale or questionnaire. Although the pertinence of this assessment may be questionable from a psychiatric point of view, this parameter, easily assessable, simple and pragmatic, seems valuable from a statistical point of view and is independent of PS and cognitive status as assessed by the MMS. In a recent study, Audisio et al. [18] showed a correlation between Geriatric Depression Scale (GDS) score and surgical morbidity. The use of GDS, a simple and validated tool to assess depression in the elderly, should certainly be recommended in further predictive studies.

The patients’ degree of autonomy, which is not directly linked to the PS, was also an independent predictor of STox. Using the Instrumental Activities of Daily Living score [19] to evaluate the autonomy of patients with hematological malignancies, one study showed this parameter to have a prognostic value for survival [20].

Concerning overall survival, we identified three baseline prognostic factors: disease stage is routinely identified but not specifically associated with older age, while retention of clinical symptoms of depression and comedictions (more than six drugs per day) confirmed the relevance of our approach. Comedication reflects comorbidity: the more drugs a patient takes, the more concomitant diseases. Frasci [21] underlined the contribution of the evaluation of comorbidities for predicting chemotherapy toxicity in lung cancer patients.

We must emphasize that chronological age, which was included in the Cox model, did not appear to have a prognostic value, in either the univariate or multivariate analysis.

Nevertheless, a potential methodological limitation in this study, other than possible patient-selection bias, was the post-chemotherapy surgical debulking performed in 14 patients, which was not taken into account. We think that this procedure did not dramatically modify our analysis of potential prognostic factors, because only responding patients, thus with better prognoses, underwent subsequent laparotomy.

Our results demonstrate that some simple parameters that can be systematically assessed in each patients >70 years old may help the physician choose the best therapeutic strategy. For patients with two or three factors predictive of poor prognosis, the use of monochemotherapy (carboplatin) should probably be chosen, in order to minimize the likelihood of STox. Best supportive care, without any specific anticancer treatment, should also be considered.

Among the limits of our methodology, the use of a possibly ‘suboptimal’ chemotherapy and the lack of standardized geriatric evaluation based on validated scales [7, 8] must be stressed.

As a consequence, GINECO has undertaken another prospective study, using the same methodology, for elderly women with advanced ovarian carcinoma, but changing the chemotherapy regimen to paclitaxel + carboplatin and conducting a more exhaustive CGA using the Instrumental Activities of Daily Living, the timed up-and-go test [22], the Prognostic Inflammatory and Nutritional Index (PINI) given by the ratio albumin x pre-albumin/C-reactive protein x orosomucoid [23], and the Hospital Anxiety and Depression Scale. The timed up-and-go test allows the investigator to assess the patient’s physical capacities in addition to autonomy and the PINI seems to provide a more accurate assessment of the patient’s nutritional status, since the biological parameters tested in our study had no evident prognostic value.
We intend to validate the usefulness of our analytical strategy to identify prognostic factors with the data being generated by the ongoing study. The coadministration of paclitaxel will be included in this analysis as a potentially prognostic variable.

In our opinion, prospective trials on elderly patients should take into account potentially prognostic items included in the CGA. As emphasized by Extermann et al. [24], some prognostic indexes need to be established to help physicians treat elderly patients. The value of those indexes could be at least equal or superior to those of the usual, clinical and biological prognostic factors used in routine oncology practice.

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References