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Prognostic factors for overall survival in elderly patients with advanced ovarian cancer treated with chemotherapy: Results of a pooled analysis of three GINECO phase II trials

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HIGHLIGHTS

- Treatment completion rates were 73% in this elderly specific population.
- Toxicities were moderate and manageable.
- Being "depressed", hypoalbuminemia <35 g/L, and FIGO stage IV impaired OS.

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ABSTRACT

Background. The GINECO led three multicentric prospective phase II studies, Elderly Woman Ovarian Trials 1 (EWOT1), EWOT2, and EWOT3, to evaluate the impact of geriatric covariates on the outcome of elderly patients treated with six courses of first-line chemotherapy for FIGO stage III—IV ovarian cancer. This pooled analysis was designed to evaluate the validity of the geriatric vulnerability parameters identified in EWOT3 (Falandry et al., 2013).

Patients and methods. From 1997 to 2011, 266 patients were recruited: 83 in EWOT1, 72 in EWOT2, and 111 in EWOT3, which evaluated respectively a 4-weekly carboplatin-cyclophosphamide regimen, a 3-weekly standard carboplatin-paclitaxel doublet and a carboplatin monotherapy. All patients were analyzed in this pooled analysis for treatment completion, toxicity, and overall survival.

Results. The global treatment completion rate was 73% and ranged from 68% in EWOT2 to 74% in EWOT3. Toxicities were generally manageable: neutropenia was more frequent in EWOT2 and thrombopenia in EWOT1 and EWOT3. In multivariate analysis, covariates associated with decreased survival were: being "depressed" according to the investigators' assessment, hypoalbuminemia <35 g/L, and FIGO stage IV. In addition, a Hospital Anxiety and Depression Scale (HADS) score >14 and Instrumental Activities of Daily Living (IADL) score <25 confirmed a deleterious impact in the EWOT2 + EWOT3 population subanalysis.

Conclusions. Despite moderate heterogeneity among the studies, this pooled analysis confirmed the deleterious effects on overall survival of emotional disorders ("depressed", as assessed by investigators or the HADS score), and decreased functionality (IADL score), in addition to FIGO stage.

1. Introduction

Epithelial ovarian cancer is the leading cause of gynecologic cancer–related deaths in Western countries [1]. There are two main reasons for the high morbidity associated with ovarian cancer. First, approximately 75% of ovarian cancer cases are diagnosed at advanced stages (International Federation of Gynecology and Obstetrics [FIGO] stages III—IV) [1]. Second, survival is related to the age at diagnosis [2,3] and the highest incidence of and mortality from ovarian cancer are reported among women 75–79 years old [4]. However, although elderly patients represent the greatest proportion of those with ovarian cancer, this population remains undertreated. Indeed, several studies show that increasing age is associated with decreased use of chemotherapy in patients with advanced ovarian cancer [5,6]. The undertreatment of

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elderly ovarian cancer patients may be attributed to the fact that treatment-related decisions are primarily based on their chronological age and not on their overall physical and mental health. Therefore, a multidisciplinary evaluation, the comprehensive geriatric assessment (CGA), was developed to identify clinical predictors of morbidity and mortality in geriatric medicine settings [7]. In the oncology setting, variables of CGA, such as functional status, may predict survival and chemotherapy toxicity [7–11].

In this context, the French National Group of Investigators for the study of Ovarian and Breast Cancer (GINECO) used the CGA to successively assess the feasibility of three different chemotherapy schedules in elderly patients with ovarian advanced cancer. Since 1997, three phase II trials incorporating the CGA have been conducted: Elderly Woman Ovarian Trials (EWOT) 1 [12], EWOT2 [13], and EWOT3 [14]. A geriatric vulnerability score (GVS) was developed on the basis of the survival score of EWOT3; the GVS integrates the following items: albuminemia <35 g/L, ADL score < 6, IADL score < 25, lymphopenia $<1 \times 10^3/mm^3$, and HADS >14 [14]. Patients having 3 or more of these vulnerability parameters are considered vulnerable. To test the validity of these geriatric prognostic factors, we performed a pooled analysis of the EWOT trials.

2. Methods

2.1. Study design

EWOT1–3 were open-label, multicenter, prospective phase II trials. Chemo-naïve elderly patients with advanced ovarian cancer were enrolled and received carboplatin and cyclophosphamide in EWOT1 (1998–2000), carboplatin and paclitaxel in EWOT2 (2001–2004), and carboplatin only in EWOT3 (2007–2011). Each trial was approved by the Independent Ethics Committee of Lyon University Hospital. EWOT2 and EWOT3 were centrally registered according 2005 guidelines (EWOT2: NCT00231075; EWOT3: INCA-RECF0456/EUDRACT 2006-005504-13). All patients provided written informed consent before participation.

2.2. Patients

Key eligibility criteria in the three trials were similar. They included age ≥ 70 years, FIGO stage III—IV ovarian epithelial carcinoma, and life expectancy of at least 3 mo (see Supplementary Text S1 for detailed inclusion and exclusion criteria).

2.3. Treatment

Patient treatments were described previously for each of the three trials [12–14]. Briefly, EWOT1 patients received carboplatin AUC (area under the curve) 5 mg min/mL and cyclophosphamide 600 mg/m^2 every 4 wk. EWOT2 patients received carboplatin AUC 5 mg min/mL and paclitaxel 175 mg/m^2 every 3 wk. EWOT3 treatment consisted of carboplatin AUC 5 mg min/mL every 3 wk. Patients received six cycles in the absence of disease progression or unacceptable toxicity. In accordance with the protocol design, treatment could be pursued upon the investigators' decision.

2.4. Comprehensive geriatric assessment

In all three trials, a CGA was performed at the inclusion visit [12–14]. CGA domains included functional status, comorbidity, emotional status, nutrition, and medication as described in Supplementary Text S2. Since our previous results demonstrated a statistical correlation between emotional disorders and lymphopenia in EWOT1 and EWOT2 (unpublished data), an association that has been previously suggested [15–17], blood lymphocyte count was also included in our explanatory model.

2.5. Toxicity

Safety data were analyzed according to the National Cancer Institute's Common Toxicity Criteria version 2.0. Severe toxicity was defined as any grade ≥ 3 toxicity.

2.6. Statistical methods

The primary endpoint of this pooled analysis was overall survival (OS), from inclusion to patient death. We used Cox proportional hazards models to determine the relationship between each covariate (i.e., patient characteristics and CGA parameters) and OS for each study. The overall pooled hazard ratio (HR) and their 95% confidence intervals (CI) were then calculated. Chi-square heterogeneity tests were carried out. I^2 statistics, expressing the proportion of variability in the results attributable to heterogeneity versus sampling error, were calculated, with I^2 statistic <25% indicating low heterogeneity, 25%–50% moderate heterogeneity, and >50% high heterogeneity. When moderate heterogeneity was observed, a random effects model was used to pool HR. In our final model, we included explanatory variables with a univariate P value of <0.10, including albuminemia (<35 vs ≥35 g/L), HADS score (>14 vs ≤14), and FIGO stage (IV vs III) as categorical variables. Reduced model selection was carried out using a backward step-down by applying the stopping rule of the Akaike information criterion. All analyses were carried out using meta-analysis packages for the R statistical software program (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient characteristics

Pooled analysis included a total of 266 patients (EWOT1, $n = 83$; EWOT2, $n = 72$; EWOT3, $n = 111$). Patient and study characteristics are summarized in Table 1. Overall, mean age was 77.1 ± 4.9 years; *performance status* was 0–1 in 61%; 28% had FIGO stage IV disease; and 25% had optimal primary surgical treatment. Despite similar inclusion criteria, there was some heterogeneity among the three patient groups. The population in EWOT3 tended to be more vulnerable than those in the two other studies, with a higher median age and a higher rate of altered *performance status* (≥2). Furthermore, the proportion of patients with optimal primary cytoreductive surgery was 16% in the EWOT3 trial versus 21% and 40%, respectively, in EWOT1 and EWOT2.

Table 1
Patient characteristics.

	EWOT1 $N = 83$	EWOT2 $N = 72$	EWOT3 $N = 111$	Total $N = 266$
Treatment years	1998–2000	2001–2004	2007–2010	1998–2012
Treatment	Carboplatin + Cyclophosphamide	Carboplatin + Paclitaxel	Carboplatin	–
Age, years				
Median [range]	76 [70–90]	75 [70–89]	78 [70–93]	76 [70–93]
Mean ± SD	76.6 ± 1.1	76.0 ± 4.4	78.1 ± 5.1	77.1 ± 4.9
Performance status	$N = 62$	$N = 72$	$N = 111$	$N = 245$
0–1 (%)	37 (60)	53 (74)	59 (53)	149 (61)
2–3 (%)	25 (40)	19 (26)	52 (47)	96 (39)
FIGO initial stage	$N = 82$	$N = 72$	$N = 110$	$N = 264$
III (%)	62 (76)	56 (78)	71 (65)	189 (72)
IV (%)	20 (24)	16 (22)	39 (35)	75 (28)
Histological subtype				
Serous papillary (%)	61 (73)	52 (71)	65 (59)	178 (67)