doi:10.1093/annonc/mdl483
Published online 17 January 2007

Is carboplatin–paclitaxel combination the standard treatment of elderly ovarian cancer patients?

Ovarian cancer is the leading cause of death from gynaecological cancer in the Western world [1]. The majority of ovarian cancer patients present with an advanced disease and show a 5-year survival rate of 25%–30%. Cytoreductive surgery combined with chemotherapy is the standard treatment of ovarian cancer. Since the 1980s clinical trials demonstrated that platinum-based chemotherapy improves survival in women with advanced disease. Carboplatin and paclitaxel association is, by now, the standard first-line chemotherapy regimen [2].

Improvement in health care and nutrition, decrease in global mortality and increasing trends of mean-life expectancy result in humans getting older compared with some decades ago. The incidence of ovarian cancer rises with advancing age, peaking in the seventh decade of life. Today, about half of all ovarian cancers occur in women over the age of 65 [1].

Elderly patients are less likely to receive optimal treatment. Moreover, comparing patients 70–79 years old with patients 80 years of age or older, Uyar et al. [3] reported that the extreme elderly had a decreased likelihood of receiving surgery and combination chemotherapy despite equivalent comorbidities.

Performing a meta-analysis, Bristow et al. [4] concluded that, during the platinum era, maximal cytoreductive surgery is one of the most powerful determinants of cohort survival among patients with advanced ovarian carcinoma. Although age is an independent prognostic factor, reduced surgical radicality contributes to poorer outcome in advanced ovarian cancer patients who are >65 years old [5]. A reason for suboptimal surgical treatment in elderly patients could be a fear of higher complication rates. In patients older than 80 years undergoing debulking surgery, Cloven et al. [6] showed high morbidity and prolonged hospitalisation, but most of the patients were discharged their home and were able to receive postoperative chemotherapy.

A recently published meta-analysis of chemotherapy regimens for ovarian cancer reported a doubling or more of time to mortality with platinum and taxane combinations [7]. Evaluating the effects of age and comorbidity on the application of treatment guidelines, Maas et al. [8] reported that even in the absence of comorbidity standard combination chemotherapy was prescribed significantly less often for elderly patients (≥70 years). Since 1983 the Eastern Cooperative Oncology Group concluded that the apparent discrimination in not treating elderly cancer patients as aggressively as younger patients did not appear to be justified [9]. In a retrospective toxicity multicentre study, chronological age did not adversely influence the ability to receive aggressive chemotherapy treatment in gynaecological malignancies [10]. Higgins et al. [11], comparing toxic effects of carboplatin and paclitaxel combination in patients less or >60 years old (60–78), concluded that age is not a barrier to the aggressive treatment of ovarian cancer with this regimen. In the study of Vilella et al. [12] women older than 70 years tolerated therapeutic doses of carboplatin and paclitaxel combination. Furthermore, platinum–paclitaxel combination is effective in elderly patients [13].

In the article published in the current issue, Tredan et al. [14] report that they do not consider carboplatin–paclitaxel (CP) combination as standard chemotherapy for elderly ovarian cancer patients. They compared two consecutive series of patient's ≥70 years old to evaluate the feasibility of two different polychemotherapy schedules. Eighty-three patients, in 30 centres, were treated with carboplatin plus cyclophosphamide (CC) administered every 4 weeks and 75 further patients, in 23 centres, received CP every 3 weeks. Comprehensive Geriatric Assessment (CGA) was carried out at study entry. More patients in the CC group presented with performance status of more than two, depression symptoms, use of comedications, hypoalbuminemia, abnormal Mini-Mental Status (MMS) score or suboptimal surgery. Both regimens appeared feasible (75.6% in the CC group and 68.1% in the CP group completed six courses) and the overall survival (OS) was similar in the two groups. Independent prognostic factors of poorer OS were: increasing age ($P = 0.013$), depression symptoms at baseline ($P < 0.001$), International Federation of Gynaecology and Obstetrics stage IV ($P = 0.001$) and use of paclitaxel ($P = 0.025$). Women in the CC group were less likely to experience neutropenia compared with the women treated by the CP combination (8.1% versus 52.8%, $P < 0.001$), but more likely to have reduced platelets (39.5% of patients with $<50 \times 10^9$/l in this group versus 9.7% in the CP group, $P < 0.001$). Low rates of grade 3–4 non-haematological toxicity were observed for both regimens, except alopecia, neurosensory and neuromotor toxicity were worse with the CP regimen. The authors concluded that the use of paclitaxel in a group of better prognosis resulted in more toxicity without evidence of improvement in OS.

The major bias of this study is the nonrandomised design, that could compromise the final results. The different schedule (4 weeks for CC and 3 weeks for CP) could underestimate the toxicity in the CC group, although the authors underline that it is comparable with most of the prospective studies evaluating the CP combination in advanced ovarian cancer. Also these data could be more precisely evaluated within a randomised trial. Furthermore, carboplatin–cyclophosphamide combination is not the standard treatment of ovarian cancer, also in elderly patients [15].

Elderly patients are less likely to be entered into clinical trials [16]. Compared with their younger counterparts, patient's ≥65 years of age with stage III/IV disease were less likely to enter into a Gynecologic Oncology Group (GOG) treatment protocol. Most common reasons were patient's ineligibility (33%), refusal (29%) and investigator decision (20%). The GOG proposed, in addition to reviewing eligibility criteria, that practitioners' attitudes should be monitored to assure elderly patients were not being inappropriately denied participation in clinical trials [17].

An interesting aspect of this trial is the evaluation of the prognostic role of CGA parameters. The authors showed previously that CGA could predict severe toxicity and OS of advanced ovarian cancer patients over the age of 70 years using the carboplatin and CC combination [18]. In the present study, CGA included evaluation of patient dependence, comedication defined as the number of different drugs taken daily (0–3, 4–6 or >6), nutritional status (total protein, albumin, prealbumin, C-reactive protein and orosomucoid) and cognitive function using the MMS; presence or absence of clinical symptoms of depression were also evaluated. The authors conclude that CGA parameters and particularly emotional disorders might help to determine a priori the risk/benefit ratio of chemotherapy. Chen et al. in a prospective pilot study reported that older cancer patients (≥70 years) undergoing chemotherapy may experience toxicity but generally are able to tolerate it with limited impact on independence, comorbidity and quality-of-life levels. They concluded that a CGA is very useful in detecting treatment-related changes in geriatric oncology patients and should be incorporated into clinical outcome analysis [19]. Prospective trials on elderly patients should take into account CGA parameters in order to predict efficacy and tolerance of treatment.

In conclusion, there is no evidence for not treating elderly ovarian cancer patients with the standard treatment or excluding them from randomised clinical trials. Carboplatin–paclitaxel combination is, by now, the standard treatment of ovarian cancer. Trials should be designed to define the better treatment of this subset of patients.

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