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Point of View

Single agents should be administered in preference to combination chemotherapy for the treatment of patients over 70 years of age with advanced ovarian carcinoma

S. Pignata [a,*], S. Monfardini [b]

[a] *Divisione di Oncologia Medica B, Istituto Nazionale Tumori, Fondazione G. Pascale, via M. Semmola, 80131 Napoli, Italy*
[b] *Divisione di Oncologia Medica, Azienda Ospedaliera di Padova, via Giustiniani 1, Padova, Italy*

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1. Introduction

The most dramatic demographic change in the 20th century has been the increase in the age of the World's population [1]. Individuals over age 65 years comprised less than 1% of the total World population in 1900, 6.2% in 1992, and are projected to be approximately 20% by 2050. This increase is most evident in developed nations [1]. The incidence of ovarian cancer rises steadily with advancing age during adult life and peaks in the seventh and eighth decades of life. Age-specific analysis reveals that the incidence of and mortality rate from ovarian cancer are continuously increasing in the elderly population [2–4].

Because ovarian cancer affects a disproportionate number of older patients, concerns arise on how 'aggressive' the radical surgery and cytotoxic therapies should be. In fact, it is commonly believed that older patients might not be able to tolerate the debilitating effects of radical surgery and chemotherapy and so it has been observed that approximately 40% of patients in their eighties were not offered a definitive cancer treatment [5]. Data from the Surveillance, Epidemiology and End Results (SEER) program database revealed that older women are less likely to be treated as intensively as younger patients [5], and that survival is dramatically affected by age [6]. So, it has been suggested that the lower survival rate of elderly patients with ovarian cancer may be related to the less intensive treatment received, although other possible explanations have been proposed in relation to different tumour biology [7] or to the more advanced stage at diagnosis due to delayed diagnosis [8]. The latter factor can significantly affect the survival rate since elderly patients are more likely to begin chemotherapy with bulky residual disease than their younger counterparts. In fact, elderly patients underwent fewer operations and a lower percentage of cases received an optimal debulking [5,9].

In this paper, we try to analyse the reasons why a single agent is preferred over a more aggressive combination chemotherapy in elderly patients with ovarian cancer.

2. Chemotherapy

The elderly population is rather heterogeneous. Age is not sufficient to define a patient and individual evaluation of physical and psychological health is necessary. Comorbidities also need to be considered. In the elderly population with cancer, approximately 55% have three additional pathologies and 37% have one or two [10]. Only 8% of elderly patients suffer from cancer alone [10]. A national survey performed in the USA in the years 1983–1988 showed that only 42% of patients $\geqslant 80$ years of age received chemotherapy after surgery, compared with 65% and 72% for those <60 years of age and 60–79 years of age, respectively [5,6]. Thus, a large number of elderly patients are undertreated and the reasons for the exclusion of treatment are not specified in this retrospective study [5].

Guidelines are clearly needed, including advice on whether to treat at all and whether to use single agents or combination therapy in elderly patients with ovarian cancer.

2.1. Efficacy and feasibility of combination chemotherapy in elderly patients with ovarian cancer

Balducci and colleagues [11] reported that elderly patients are at increased risk for haematopoietic,

* Corresponding author. Tel.: +39-81-590-3269; fax: +39-81-590-3822.
E-mail address: pignata@sirio-oncology.it (S. Pignata).

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mucosal, cardiac and neurological complications from chemotherapy. The data on the feasibility of combination chemotherapy in elderly patients with ovarian cancer are scarce and are mainly derived from phase II and III studies carried out in the general population of patients with ovarian cancer. Furthermore, the collection of information on clinical trials in elderly cancer patients is slow since these patients are often excluded from clinical studies in ovarian cancer.

Nonetheless, some studies suggest that elderly patients with ovarian cancer should receive standard combination chemotherapy since toxicity is not significantly increased by their age. This point of view is based on the analysis of toxicity recorded in the few elderly patients treated in multicentre clinical trials performed on the general population of ovarian cancer patients mainly in the USA [12–14]. Table 1 shows the data from the three main studies published on combination chemotherapy in elderly patients with ovarian cancer. All these trials showed a poorer prognosis in elderly patients with respect to their younger counterparts; however, all three studies concluded that a standard combination chemotherapy treatment should not be denied to aged patients considering the worse prognosis and the acceptable level of toxicity. However, one of the main problems in establishing guidelines on the basis of the findings of these clinical trials is that the conclusions of the tolerability of chemotherapy in elderly patients can be applied only to those selected cases entered in randomised trials. In fact, the findings of the Sloan Kettering Cancer Center [15] have shown that patients >65 years of age who underwent initial surgery for ovarian cancer were significantly less likely to enter an experimental treatment programme compared with patients <65 years of age. Although a number of specific comorbid medical conditions could be identified as possible explanations for this observation, most frequently a history of cardiovascular disease, for a significant number of cases it was not possible to determine a reason for patient exclusion. It is reasonable to speculate that many elderly patients are not entered into more intensive treatment regimens because of their chronological age rather than because of specific comorbid medical conditions. None of the reports summarised in Table 1 regarding the elderly patients included in randomised studies indicates the number of ineligible patients nor the reasons for ineligibility [12–14]. Comparing the percentage of elderly patients included in randomised trials with the incidence and mortality rate, in this age group, it appears that the percentage of patients $\geqslant 65$ years is lower than expected, strongly suggesting that older patients are underrepresented in cancer treatment trials [16]. This *a priori* selection leads us to believe that available information from most studies on elderly patients has probably been collected from patients with a younger biological age than that of the whole population of elderly patients with cancer. Thus, the indications of combination chemotherapy as standard therapy in elderly women with ovarian cancer is based mainly on data from studies performed in selected cases and excludes a large percentage of elderly patients.

Another major point of concern is that all three studies in Table 1 described the toxicity level separately in patients over and under 65 years of age. The elderly population is rather heterogeneous and also the chronological age should have been more precisely specified. The American National Institute of Ageing defines three age categories of elderly: 65–74 years, 75–84 years and 85 years or over. The tolerability to chemotherapy is significantly different amongst these age groups. The European Organization for Research and Treatment of Cancer Study Group on Neoplasia in the Elderly has recently addressed the topic of chemotherapy in older patients [17]. Whilst standard treatment can usually be applied to elderly patients up to age 70 years, in cases where the patients are over 70 years, few data are available about the tolerability of the majority of the

Table 1
Tolerability of combination chemotherapy in elderly patients with ovarian cancer

Author [Ref]	Alberts [12]	Thigpen [13]	Edmonson [14]
Group	SWOG	GOG	Mayo
Type of study	Phase III	Phase III	Phase III
Combination chemotherapy used	Cisplatin Cyclophosphamide Doxorubicin	Cisplatin Cyclophosphamide	Cisplatin Cyclophosphamide Doxorubicin
Total patients	342	1592	383
Pts >65 years	123	512	65
Pts >70 years	n.a.[a]	173	n.a.
Dose intensity	=	=	↓ over 65
Total dose delivered	↓ over 65	↓ over 65	↓ over 65
Haematological toxicity	↑ over 65	↑ over 65	–
Non-haematological toxicity	=	=	=

[a] n.a., not available.

Table 2
Randomised studies comparing single-agent platinum compound versus combination chemotherapy[a]

Author [Ref]	[20]	Skarlos [21]	Muggia [22]	Parmar [19]
Group	GICOG	Hellenic cooperative group	GOG	ICON 2
Type of study	Phase III	Phase III	Phase III	Phase III
Drugs used	Cisplatin versus CAP versus CP	Carboplatin versus carboplatin, epirubicin, cyclophosphamide	Cisplatin versus paclitaxel versus cisplatin + paclitaxel	Carboplatin versus CAP
Total patients	565	130	648	1526
Response rate	↑ CAP	–	↑ paclitaxel	
Haematological toxicity	↑ CAP	↑ CEP	–	↑ CAP
Survival	=	=	=	=

[a] CAP, cisplatin, cyclophosphamide, doxorubicin; CP, cisplatin, cyclophosphamide; CEP, cisplatin, cyclophosphamide, epirubicin.

drugs. The use of a multidimensional geriatric evaluation has been proposed for patients not entered into a clinical trial [18]. This geriatric evaluation is used to develop the best therapeutic plan for each individual patient, taking into account family support, mental status, the type and degree of disability and the presence of comorbidities [18].

It is our opinion that properly designed clinical trials should be performed in elderly patients with ovarian cancer, assessing the tolerability of chemotherapy in relation to a geriatric multidimensional evaluation, before it is possible to generally suggest combination chemotherapy for patients over 70 years.

2.2. What do we know about the efficacy of single-agent chemotherapy in ovarian cancer?

A series of meta-analyses of randomised controlled trials raised the question of whether the multidrug combination was more effective than optimal dose single-agent carboplatin for women with advanced ovarian cancer. The multicentre international study ICON 2 has compared single-agent carboplatin with the three-drug combination (cyclophosphamide, doxorubicin and cisplatin) CAP [19]. The final results indicate that there is no evidence that CAP is more effective than carboplatin: in fact, although CAP was shown to be more toxic, no benefit in survival was observed. This study indicates that single-agent carboplatin is a safe and appropriate treatment for women with advanced ovarian cancer. The large ICON2 series enabled the analysis of subgroups and there was no evidence that CAP was more effective in any patient group [19]. In particular, no evidence of a better effect of combination chemotherapy was found in patients with optimal versus sub-optimal debulking [19], a condition that frequently occurs in the elderly [5]. Other studies have clearly defined the activity of single-agent carboplatin in patients with ovarian cancer [20,21]. The main studies are summarised in Table 2 which also shows the Gynaecology Oncology Group trial (GOG132) results, indicating that cisplatin alone induces the same survival rate as the combination of paclitaxel and cisplatin [22].

Carboplatin administered as a single agent is very safe, and it has been shown that elderly patients >60 and >70 years tolerate well the same dose intensity as their counterparts without the need of schedule modifications [23]. On the basis of the documented activity and safety of carboplatin, we think that single-agent carboplatin can be considered the standard treatment in patients with ovarian cancer over 70–75 years old. The safety profile suggests that a better effect on the quality of life can be obtained with respect to combination chemotherapy as has recently been demonstrated in lung cancer with single-agent chemotherapy [24].

Several phase II studies have showed a high response rate of paclitaxel in untreated patients with ovarian cancer with an objective response rate ranging from 50 to 61% [25–27]. It was demonstrated that elderly patients with ovarian cancer treated with single-agent paclitaxel did not differ from younger patients with respect to administered dose intensity, number of cycles administered or the occurrence of serious or mild toxicities [28]. Since paclitaxel has an extensive non-renal clearance it could be considered as a possible single-agent treatment in patients with impairment of renal function that can increase carboplatin toxicity. In this setting, it has been demonstrated that paclitaxel can be administered weekly with a favourable toxicity profile and a dose-intense delivery of the drug [25]. The tolerability and activity of weekly paclitaxel in elderly patients with ovarian cancer may represent a possible focus for research in future years.

3. Conclusions

In our opinion, available data do not support the use of combination chemotherapy in elderly patients. Data on tolerability of combination chemotherapy in aged patients with ovarian cancer are scarce and are on selected elderly patients enrolled in randomised studies

performed in the general population of cancer patients. Furthermore, very few data are available about the tolerability of combination chemotherapy in patients over 75 years old. Properly designed clinical trials should be performed in elderly patients with ovarian cancer assessing the tolerability of combination chemotherapy in relation to a geriatric multidimensional evaluation.

Carboplatin administered alone is an appropriate and safe treatment for women with advanced ovarian cancer and is well tolerated in elderly patients. On this basis, we suggest that single-agent carboplatin can be considered the standard treatment in elderly patients over 70 years.

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