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Consensus Statement

A new standard of care for treatment of ovarian cancer

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1. Introduction

Ovarian cancer is the second most frequent gynaecological cancer in Western Europe and causes approximately 82 000 deaths per year. The majority of patients present with advanced disease and require a combination of surgery and chemotherapy. Important features that determine the outcome of treatment include the stage of disease and the size of the residual tumour after initial surgery. Women with sub-optimally debulked tumours (residual tumour nodules >1 cm) have a poorer prognosis than women whose tumours have been optimally debulked.

In recent years several large randomised studies, comparing a variety of platinum-based chemotherapy regimens, have been performed in women with advanced ovarian cancer. Data from these studies are now available and the broad consensus is that what constitutes standard practice needs to be re-evaluated.

2. History

It has been universally accepted for many years that patients with advanced ovarian cancer require a platinum compound. Meta-analysis involving 1200 patients suggested a small, but statistically significant survival advantage for combination platinum chemotherapy [1] and, therefore, in many countries, the combination of cisplatin and cyclophosphamide was considered the standard regimen. In order to avoid the toxicity of cisplatin many investigators utilised carboplatin instead because it is less emetogenic and causes less nephro-, oto- and neurotoxicity than the parent compound, although it is more myelosuppressive. The possible benefits of adding another drug such as doxorubicin to the platinum–cyclophosphamide combination was addressed in several randomised trials [2–4]. These studies could not definitively prove a survival advantage for the inclusion of doxorubicin but two meta-analyses [5, 6] suggested such a benefit. Further evidence is provided by the long-term follow-up data on optimally debulked patients in a study of the Gynaecologic Oncology Group (GOG 052) which, was part of these meta-analyses [7].

In contrast, interim results from the largest international study ever conducted in ovarian cancer (ICON-2) did not find a significant survival difference between patients treated with single-agent carboplatin or a combination of cisplatin, doxorubicin and cyclophosphamide [8]. Many centres in the UK, therefore, continued to use carboplatin alone as the standard of care. Data from the final analysis of this trial are awaited and there have been criticisms of the doses of the drugs that were used. Other attempts to improve the results of treatment have included increasing the dose intensity of platinum, but these have so far failed. Improvements in overall survival have now been seen following the introduction of the drug paclitaxel. Two large randomised trials have compared the combination cisplatin–cyclophosphamide with cisplatin–paclitaxel [9, 10]. Both studies demonstrated a statistically and clinically significant advantage in terms of response rates, progression-free and, most importantly, overall survival for the paclitaxel–cisplatin combinations. Subset analysis suggests that the survival benefit applies both to women with optimally and suboptimally debulked tumours [10]. As a result and in line with 'evidence-based' medicine criteria, the combination of paclitaxel–cisplatin is today's gold standard regimen for patients with newly diagnosed advanced ovarian cancer [11].

A third study randomised patients to receive single-agent cisplatin or paclitaxel at doses slightly above standard, 100 mg/m^2 and 200 mg/m^2, respectively, or a

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combination of the two at standard dose [12]. There was no advantage to patients treated with the cisplatin–paclitaxel combination in terms of progression-free or overall survival compared with those treated in the other two arms of the study. However, the great majority of patients (approximately 90%) treated on the single-agent arms of the trial eventually received salvage therapy. Of those, approximately 50%, crossed over from the single agent prior to the onset of clinical progression. Crucially, approximately half the patients randomised to single-agent treatment crossed over to the other compound before progression occurred. Therefore, this trial was a comparison of the combination of cisplatin and paclitaxel versus their sequential use. In view of the better tolerance of the combination, the investigators themselves stated that these results should not be used as an argument against the adoption of cisplatin–paclitaxel as standard therapy. The same comment applies to the premature and largely provocative results of ICON-3 presented at the 1999 ASCO meeting [13]. From this large trial, there was no apparent overall advantage to the carboplatin–paclitaxel combination in comparison with carboplatin as a single agent or 'CAP' (cyclophosphamide, doxorubicin, cisplatin). However, follow-up was only 18 months and this is much too short to make meaningful conclusions at this stage.

3. Optimal scheduling of paclitaxel

The optimal dose and scheduling of paclitaxel when in combination with cisplatin remains a matter of debate. The first study in previously untreated patients utilised a dose of 135 mg/m^2 administered over 24 h because preclinical data suggested that prolonged infusions were more effective. The main side-effects of this regimen included the incidence of complicated neutropenia and grade 3–4 neuropathy in approximately 5% of patients. The second, confirmatory study used a 3-h schedule at a dose of 175–200 mg/m^2 based on data from a large randomised trial of patients with relapsed ovarian cancer which did not demonstrate a dose– or schedule–response relationship. This study showed that there were no significant differences between 3-h compared with 24-h infusion schedules or a dose of 175 mg/m^2 of paclitaxel compared with 135 mg/m^2 [14]. In previously untreated patients, the combination of paclitaxel 175 mg/m^2 over 3 h and cisplatin 75 mg/m^2 resulted in grade 3–4 neurotoxicity in 19% of patients in contrast to $<5\%$ of patients when cisplatin was combined with paclitaxel at 135 mg/m^2 over 24 h [10]. However, caution is needed in making this comparison, since more cycles of treatment were given to patients in the former trial (up to nine cycles as opposed to a maximum of six).

4. Choice of platinum analogue

Cisplatin is associated with serious side-effects as previously stated and, therefore, many prefer to use the less toxic analogue carboplatin. A large meta-analysis has shown that cisplatin and carboplatin are equally effective [15]. It is generally accepted that even if a difference does exist, it is likely to be small and carboplatin would still be the preferred platinum analogue for suboptimally debulked patients because of its significantly better toxicity profile and the incurability of this group of patients. When carboplatin is substituted for cisplatin within the context of platinum–paclitaxel therapy the latter is administered at a dose of 175 mg/m^2 over 3 h to avoid myelotoxicity [16–18]. This has the additional advantage of allowing the regimen to be administered in the outpatient setting.

Several studies have now compared carboplatin–paclitaxel regimens with cisplatin–paclitaxel regimens. Three randomised studies have presented their initial results, a Dutch–Danish collaborative trial, the German AGO Study and a GOG Trial (GOG 158) [19–21]. They show that it is feasible to substitute carboplatin for cisplatin in the paclitaxel combination without major problems and with the regimen being administered as outpatient therapy. Furthermore, carboplatin–paclitaxel was significantly superior compared with cisplatin–paclitaxel (3-h schedule) in terms of quality-of-life during chemotherapy, inducing significantly less neurotoxicity and emesis. The three studies reported very similar response rates, progression-free and overall survival although more mature data on overall survival are required before there is certainty about the equivalence of the two regimens.

5. Conclusions

There is no doubt that in 1998 the best survival results for patients with advanced ovarian cancer are obtained with upfront use of cisplatin and paclitaxel. The preferred regimen for the treatment of ovarian cancer should not only provide the best long-term survival rates but also meaningful palliation and acceptable quality of life for the majority of women with a less favourable prognosis. In this respect, side-effects of treatment must be minimal with admissions to hospital avoided wherever possible [22]. Carboplatin–paclitaxel could fulfil these criteria if long-term survival data from the carboplatin–paclitaxel versus cisplatin–paclitaxel studies show equivalent results. So far, survival differences have not been detected after 2 years' follow-up and, therefore, in view of its superior therapeutic index, carboplatin-paclitaxel appears an acceptable treatment option for the treatment of advanced ovarian cancer patients. We will soon learn whether carboplatin–

paclitaxel is the new 'gold standard' regimen for all patients. In the meantime, studies continue to investigate ways to optimise the schedule of platinum–paclitaxel combinations and to evaluate the incorporation of other active drugs, such as doxorubicin, into these regimens.

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