Abstract

Ovarian and cervical cancers are significant health problems. This article provides an update in selected management topics. Paclitaxel and platinum derivatives are the first-line treatment for patients with advanced disease. In selected patients, intraperitoneal chemotherapy has been associated with improved survival but the broad applicability of this strategy is limited by issues of toxicity and feasibility. Management of patients with recurrent disease is based on a number of factors and includes surgery in selected cases, platinum-based chemotherapy for patients with platinum-sensitive disease and other agents such as topotecan and pegylated liposomal formulation of doxorubicin for patients with platinum-resistant disease. In cervical cancer, the most significant issue/event is the demonstration of superior survival with topotecan and cisplatin compared to cisplatin alone. Finally, new agents such as epidermal growth factor receptor inhibitors and antiangiogenic agents are being currently tested in these settings.

Key words

Ovarian cancer • Chemotherapy • Cervical cancer • Update

Introduction

Ovarian cancer (OC) is the leading cause of death from gynaecologic malignancies and represents the fourth leading cause of death from cancer in general in women, affecting more than 3000 women per year in Spain. Because early-stage OC is generally asymptomatic, approximately 70% of women present with advanced disease at diagnosis. Survival is highly dependent on stage of disease: 5-year survival in patients with early-stage is 80–90% compared to 20–30% for patients with advanced-stage. Therefore there is a justified need to search for new treatment strategies.

On November 2006, a group of OC experts met in Barcelona, Spain, to discuss important controversial topics in the management of patients with ovarian and cervical cancers. The areas covered included management of patients with newly diagnosed OC, role of intraperitoneal (IP) chemotherapy (CT), management of patients with recurrent disease, update in cervical cancer and novel targeted agents. This paper summarises the main points discussed at the meeting.
GOG 104, GOG 114 and GOG 172. Though these studies have a similar design, GOG 104 did not include taxanes and the two more recent studies required, as inclusion criteria, a residual disease of <1 cm. Overall, the results showed that IP administration was associated with an increase in progression-free survival of five months and an increase in overall survival that ranged from 8 to 16 months. Though globally the results of GOG 104 were inferior, when the subgroup of patients with residual disease of <1 cm were analysed separately, equivalent results were obtained. Proportionally, the 4-year survival increased 4–10%, which is similar to the results achieved with adjuvant treatments for breast, lung and colon cancers. A recent meta-analysis of the published trials favours the use of IP CT [6].

IP administration is associated with major toxicity that includes haematological, neurological and renal manifestations. The most important complications, nevertheless, are catheter-related, such as bacterial infections, blockades, leaks and pain. In the most recent study, GOG 172, these complications resulted in 40% of patients withdrawing before completing six cycles of treatment. Though this study demonstrated an increase in overall survival of 16 months, the study has several controversial issues [7]. The first one is the choice of paclitaxel and cisplatin as control arm instead of paclitaxel and carboplatin, which is the current standard regimen and achieves a mean survival of 57.4 months. Secondly, both treatment arms not only differed in the route of administration but also in the dose intensity, as patients treated with IP CT also received intravenous paclitaxel and a higher dose of cisplatin. It is striking that no increase in disease-free survival was observed and this could be due to differences in the second-line treatments utilised. Patients that did not tolerate one treatment scheme could switch to the other one and replace cisplatin for carboplatin, therefore complicating the interpretation of the results. Finally, the patients were very selected and treatment with IP CT was more toxic.

There are different opinions regarding the acceptance of IP CT as standard treatment. Although the results regarding higher survival in most of the recent studies are clinically significant, the methodological limitations previously discussed reduce their impact. The main limitation of this strategy is that it is only applicable to a relatively small number of patients that includes those with stage III disease, optimal surgery, very good performance status and those that are willing to undergo IP treatment. For the rest of the patients, representing most of the cases, this treatment is not applicable. IP administration requires some resources that are not available in most of the hospitals, including outpatient clinics with a wide schedule of operating hours, hospitalisation beds and an interdisciplinary on-call team integrated by oncologists and surgeons [8].

It can be concluded that IP administration of CT may have an important role in the treatment of OC in a very selected group of patients. Nevertheless, the methodological limitations of the current studies and the toxicity associated with the treatment as well as the resources required for its administration limit its broad applicability.

**Prolongation of platinum-free interval and management of patients that present intermediate recurrences (6–12 months) of ovarian cancer**

The first-line treatment of patients with stage III and IV OC includes combination CT regimens with platinum and taxanes. Despite the initial high tumour response rates, most of the patients relapse. After relapse, the outcome of patients depends on many factors including performance status, CA-125 levels, number of tumoral locations, tumour volume, histological type and platinum-free interval (PFI) [9, 10]. Some studies have demonstrated that the response rate to second-line CT treatments in patients with PFI >24 months is >70%, whereas in those with PFI <12 months it is approximately 30%. Response rates are even lower in those patients with early recurrences (PFI <5 months) [11-13]. Although the most widely accepted classification that defines platinum resistance includes those patients who progress with a PFI <6 months, frequently recurrences are classified in refractory, resistant, sensitive or very sensitive to platinum depending on PFI (<4 months, 4–6 months, 6–12 months and >12 months, respectively). There is a consensus that patients with very sensitive recurrences must be re-treated with platinum-containing regimens. Likewise, patients with refractory or resistant relapses must receive other non-platinum drugs or regimens. However, the management of patients with sensitive relapses is more controversial.

Platinum resistance is a complex phenomenon in which biological factors such as expression of membrane efflux pumps (MDR), development of mechanisms of resistance to apoptosis (p53 and bcl-2) and increase in DNA repair intervene [14]. These mechanisms have a dynamic nature and can evolve over time. This concept has important therapeutic consequences because it suggests that prolongation of the PFS could influence the resistance to platinum compounds. Hence, the strategy in patients with PFI of 6–12 months would be the administration of a drug with a different mechanism of action, without resistance or crossed toxicities that prolonged PFI for more than 12 months allowing the reintroduction of platinum-based regimens [15]. This concept is supported by the results of phase II studies in which patients with platinum-resistant disease received platinum-based regimens in the third line and an increase in the response rate was observed in patients with longer PFS during the second-line treatment administration [16, 17].