Medical treatment of resistant or recurrent epithelial ovarian cancer

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Epidemiologic analysis reveals that mortality rates from ovarian cancer are continuously decreasing due to the improvement of surgery and chemotherapy. However, overall, the prognosis of ovarian cancer patients is still unsatisfactory considering that only 30\% of the patients are alive after 5 years. In fact, although surgery and first-line systemic chemotherapy induce complete and partial response in up to 80\% of patients, with about a 25\% pathological complete remission rate, recurrences occur in the majority of patients. Most of these patients are subject to repetitive treatment cycles that, although palliative in nature, are also able to prolong survival. Important results have been obtained, in particular in platinum sensitive recurrent disease where a platinum base chemotherapy is able to prolong progression-free survival and overall survival. Overall, our armamentarium for the treatment of progressive or recurrent ovarian cancer is significantly richer than in the past, and in many patients it is possible to achieve the objective to reach a chronic history of the disease.

**Key words:** ovarian cancer, chemotherapy

**introduction**

The standard initial treatment of patients with advanced ovarian cancer is cytoreductive surgery, followed by combination chemotherapy with paclitaxel and a platinum compound \cite{1, 2}. Despite the activity of this combination chemotherapy, which gives response rates up to 80\%, the majority of patients die of their recurrent disease \cite{3}. Therefore, a large proportion of patients are candidates for second-line therapy.

Patients who progress on first-line therapy or relapse within 3 months are considered to be refractory to a platinum re-treatment \cite{4}. Patients who respond to primary treatment and relapse within 6 months are considered platinum resistant \cite{4}. Patients who relapse more than 6 months after completion of initial therapy are characterized as platinum sensitive \cite{4}.

**treatment of platinum refractory/resistant ovarian cancer**

Refractory/resistant ovarian cancers are not considered suitable for secondary surgical cytoreduction and their treatment is medical. However, the value of a second-line therapy and its impact on survival is modest \cite{4, 5}. Agents such as epirubicin \cite{6, 7} and etoposide \cite{8} and those with the more recent active drugs topotecan \cite{9}, stealth liposomal doxorubicin \cite{10} and gemcitabine \cite{11} show response rates ranging from 10\% to 25\%, but lengthy remissions are infrequent \cite{5}. Thus, the treatment of these patients remains a challenge for the near future and there is a need for studies with new drugs.

Liposomal doxorubicin is considered the single agent first choice in these patients. The drug is a preparation of doxorubicin hydrochloridic acid in pegylated liposomes that confers a much longer half-life in blood and a different profile of toxicity than doxorubicin \cite{12}. The surface of pegylated liposome is coated with methoxypolyethylene glycol polymers, which prevent liposomal detection and destruction by the reticuloendothelial system \cite{13}. The pegylated liposomes are small (about 100 nm in diameter) and can pass through endothelial gaps or leaky membranes commonly associated with tumors \cite{14}. In a phase III study Gordon et al. \cite{10} have recently shown in a population of patients progressed or recurred within 12 months that liposomal doxorubicin is at least as effective as topotecan in platinum refractory-resistant ovarian cancer with a statistically significant survival advantage in platinum-sensitive patients. The toxicity profile of liposomal doxorubicin was significantly better compared to topotecan. An ongoing study from the MITO group is comparing, in the same setting, liposomal doxorubicin with gemcitabine, but results are not yet available.

In this subgroup of patients it has not been demonstrated that combination chemotherapy is better than single agents. The few studies performed showed increased toxicity without any impact on survival, although studies with the new drugs have not been performed. Recently, interesting experiences have been published with the combination of stealth liposome...
doxorubicin with vinorelbine [15] or gemcitabine [16]. Phase 3 data are needed, although activity and toxicity results seem very promising.

**treatment of platinum sensitive ovarian cancer**

The increase in Ca125 levels is often the first sign of recurrence without confirmatory imaging. There is no data indicating that early treatment at Ca125 increase improves survival compared with delayed treatment at clinical or radiological relapse, although a trial from EORTC is ongoing. According to current dogma, sensitivity to a new treatment with platinum increases proportional to platinum-free interval, being maximal after 18 months [4]. As optimal cytoreduction is considered a major goal of treatment in the first-line setting, it has been proposed that a secondary cytoreduction may improve survival also in patients with sensitive recurrences. No prospective randomized data is available, but retrospective series suggest that when a cytoreduction with no residual disease is achieved this can significantly impact on survival. The problem of patient selection for surgery is crucial and predictive scores have recently been proposed and will be validated in future trials.

Two large randomized studies in platinum-sensitive disease have demonstrated that the addition of a second drug to carboplatin improve the outcome of the patients. The ICON4/AGO2.2 trial [17] compared a platinum-based chemotherapy (70% carboplatin alone) with a carboplatin and paclitaxel combination. In this study, which enrolled 802 patients, there was an absolute difference in 1-year progression-free survival of 10% and in 2-year survival of 7%. The combination induced an acceptable toxicity profile with neurotoxicity (20% grade 2–4) as the major compliant. This can represent a limit since it has been shown that a significant proportion of recurrent patients have residual neurotoxicity coming from first-line treatment.

Similar results have been obtained with the combination of carboplatin and gemcitabine versus carboplatin [18]. In the AGO study, the combination significantly improved progression-free survival along with a better quality of life. Toxicity was prevalently hematological, while neurotoxicity was of a lower degree.

An important phase III study from the Gineco and the GCIG is now comparing carboplatin and paclitaxel versus carboplatin and liposomal doxorubicin. This latter combination chemotherapy proved to be highly effective in a phase II French study, with a very safe toxicity profile.

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**references**