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Current Study Concepts for Refractory Ovarian Carcinoma

Key Words
Ovarian cancer · Recurrence therapy · Study concepts second-line

Summary
Second-line and recurrence therapy in advanced ovarian carcinoma is at present based more on clinical empiricism than on data from prospective comparative studies. The resulting uncertainty with respect to optimum treatment can only be removed by consistent and systematic clinical research. For this reason, the Ovarian Carcinoma Study Group in the 'Arbeitsgemeinschaft Onkologie' (AGO) has decided to offer various studies not only for primary therapy but also for second- and third-line situations where differentiation is made in patients after paclitaxel/platinum pretreatment between women with platinum-refractory carcinomas and recurrence up to 6 months after completion of primary therapy, on the one hand, and patients with platinum-sensitive carcinomas with recurrence later than 12 months after completing primary therapy, on the other hand. In addition, a newly defined group with intermediate prognosis in whom the recurrence occurs between 6 and 12 months after completion of primary therapy has been included. A prospective randomized study is offered for each of these patient groups in which patients with platinum/paclitaxel pretreatment can be enrolled. Only the coherent evaluation of various treatment modalities can lead to an improvement in the quality of therapy in second- and third-line situations.

Schlüsselwörter
Ovarialkarzinom · Rezidivtherapie · Studienkonzepte Second-line

Zusammenfassung
Die Second-line- und Rezidivtherapie beim fortgeschrittenen Ovarialkarzinom basiert zur Zeit mehr auf klinischer Empirie als auf Daten prospektiver Vergleichsstudien. Die daraus folgende Unsicherheit bezüglich einer optimalen Therapie kann nur durch konsequente und systematische klinische Forschung behoben werden. Deshalb hat sich die Studiengruppe Ovarialkarzinom innerhalb der Arbeitsgemeinschaft Onkologie (AGO) entschlossen, nicht nur für die Primärtherapie, sondern auch für die Second- und Third-line-Situation verschiedene Studien anzubieten. Bei Patientinnen nach Paclitaxel/Platin-Vorbehandlung wird hier unterschieden zwischen Frauen mit platinrefraktärem Karzinom und Rezidiv bis 6 Monate nach Abschluß der Primärtherapie einerseits und Patientinnen mit platinsensiblem Karzinom mit Auftreten eines Rezidivs später als 12 Monate nach Abschluß der Primärtherapie andererseits. Zusätzlich neu definiert wurde die sogenannte prognostisch intermediäre Gruppe, bei der das Rezidiv zwischen 6 und 12 Monate nach Abschluß der Primärtherapie auftritt. Für jede dieser Patientengruppen wird eine prospektiv randomisierte Studie angeboten, in die Patientinnen mit Platin/Paclitaxel-Vorbehandlung eingebracht werden können. Nur durch die konsequente Evaluierung der verschiedenen Therapiemodalitäten kann es zu einer Verbesserung der Therapiequalität in der Second- und Third-line-Therapie kommen.

Introduction

When primary therapy of ovarian carcinoma fails, a cure is generally impossible or extremely unlikely. Depending on the time of recurrence, however, successful palliative treatment is quite possible which, in addition to prolongation of life or the disease-free interval, usually chiefly produces an improvement in quality of life. With reference to the last point in particular, treatments are necessary that are still effective after platinum pretreatment and which also have the lowest possible toxicity. Up to now, it has generally been the rule to define two recurrence groups with different prognoses depending on the response to their primary platinum-containing chemotherapy. Patients who experience progression on chemotherapy with a platinum agent or who have a recurrence within 6 months of completing primary therapy are defined to have platinum-refractory ovarian carcinoma. Patients with 'platinum-sensitive' ovarian carcinoma are those in whom a treatment-free interval

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of at least 6 months can be achieved after response to primary therapy.

By including paclitaxel in the primary therapy, it has been possible to significantly prolong both progression-free and overall survival rates in patients with residual tumors in comparison to patients who previously had received standard therapy consisting of platinum analogs and cyclophosphamide. The improvements are, however, bought at the cost of higher toxicity rates, which are more or less pronounced depending on whether cisplatin or carboplatin was used as the combination partner. Thus, a not insubstantial percentage of patients who received primary therapy with platinum and paclitaxel exhibited considerable neurotoxicity which was still objectively demonstrable even several months after completing primary therapy. These patients are usually not willing to undergo renewed platinum/paclitaxel therapy in the case of recurrence within 12 months after completion of primary therapy. Therefore it is usefull to re-evaluate or redefine the original classification into only two different prognostic groups at risk of recurrence. In addition to the platinum-resistant and platinum-sensitive ovarian carcinomas, it would be reasonable to define an intermediate prognostic group of patients who relapse within a period of 6 and 12 months after completion of primary chemotherapy with platinum/paclitaxel.

The response rates to treatment in platinum-refractory ovarian carcinomas are generally poor and remission rates of more than 20% are rare. Therefore, especially in this situation, it is important to use agents with an optimal side-effect profile and low toxicity. To what extent one resorts to long-known drugs such as treosulfan, etoposide, hexamethylmelamine, epirubicin, cyclophosphamide or one uses newer substances such as topotecan, gemcitabine, vinorelbine or liposomal doxorubicin must generally be decided individually according to the current evidence in the literature. The survival data are poor, even in studies yielding better results, and generally predict less than 1 year. These overall poor results show that the assessment of the response rate in such patients is not necessarily equivalent to the efficacy of the treatment. As there is only a very slight survival advantage, even in situations with an initially high response rate, aspects such as quality of life during treatment or the spectrum of side effects gain increasing importance. As the assessment of all these aspects can only be reliably carried out in comparative prospective randomized studies, various treatment concepts for second- and third-line therapy of ovarian carcinoma have been developed for the Ovarian Carcinoma Study Group within the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO). All of these studies are characterized by effective monitoring and obligatory documentation of quality of life.

Platinum-Refractory Carcinoma

In platinum-refractory ovarian carcinoma with recurrence during primary therapy or within 6 months of its completion, the overall unsatisfactory results merit consideration of other alternative treatments. One possibility in this situation are endocrine forms of treatment, such as GnRH analogs, tamoxifen or gestagens.

Study of Treosulfan versus Leuprorelin Acetate

The study of treosulfan 7 g/m^2, day 1, versus leuprorelin acetate 3.75 mg, day 1, every 4 weeks was initiated by the Ovarian Carcinoma Study Group for this group of patients. Here the question of prime interest was whether the probably low-side-effect endocrine therapy is equivalent to chemotherapy with treosulfan, also considered to be mild. Leuprorelin acetate was selected because previous studies had demonstrated at least a certain degree of response. In principle, tamoxifen showed approximately equivalent response rates with an equally low side-effect rate, but leuprorelin was given preference in the end. While gestagens show an excellent roborant effect, this group of drugs was not considered as the reference substance because of their considerably lower response rate of 3%.

Ovarian Carcinoma with Intermediate Prognosis

For these patients who relapse within 6 to 12 months after completion of primary therapy, re-induction with platinum analogs can be considered. As already mentioned above, however, many patients reject restarting treatment with the primarily used agents because of the persistent toxicity.

Study of Topotecan versus Treosulfan

There are only few studies available on second-line therapy after platinum/paclitaxel pretreatment. In view of the current data situation it therefore seems reasonable to compare agents with low side effects on the one hand and new substances on the other. To this aim, the Ovarian Carcinoma Study group within the AGO has initiated a study comparing treosulfan 7 g/m^2, day 1, and topotecan 1.5 mg/m^2, days 1–5, with respect to survival, toxicity and, especially, quality of life. Secondary criteria are progression-free survival and the remission rate. Inclusion criteria for this study are initial proof of an epithelial ovarian tumor, platinum/paclitaxel pretreatment, and recurrence within 6 to 12 months after completion of primary chemotherapy. Exclusion criteria are – as commonly defined – secondary malignancies, pretreatment with more than one chemotherapy regimen in a second-line situation, and serious medical diseases. If hematological side effects occur, the dose should be reduced initially. The addition of G-CSF is not envisaged for the primary study. Indications for dose reduction are febrile neutropenia or grade IV thrombocytopenia. A reduction of the neutrophils to less than 500 for more than 5 days or less than 100 for more than 3 days are reasons for dose reduction, which is carried out from an initial level of 1.5 mg/m^2 topotecan in increments of 0.25 mg each to 1 mg/m^2. Treosulfan is reduced from an initial dose of 7 g/m^2 to 5 or 4 g/m^2. If the treatment cannot be adequately administered in spite of corresponding reductions, the study must be terminated. Further criteria for dropout were defined as the patient's wishes first of all, then intolerable side effects and disease progression during therapy.

This study is also available for patients in a third-line situation, i.e., those in whom platinum re-induction has already been carried out for late recurrence after primary therapy with platinum or paclitaxel. Here the starting doses, however, are 1.25 mg/m^2 of topotecan and 5 g/m^2 of treosulfan. When marked

hematological side-effects occur, the dose is reduced once initially followed by discontinuation of the study if the therapy cannot be adequately carried out.
In principle, these two patient populations, i.e. with recurrence 6 to 12 months after completion of therapy or progression after re-induction of platinum for late recurrence, involve the same basic situation. The prognosis for both the patients who develop a recurrence 6 to 12 months after primary therapy and those who have shown renewed progression after platinum re-induction for late recurrences can be regarded as being approximately the same. With respect to the side-effect rate and therapeutic response, however, this study will be stratified into second- and third-line. The essential difference is marked in the initial dosage, as more hematological side effects are to be expected in the third-line situation. Recruitment is planned to include a total of 120 patients over 2 years; 45 patients have already been enrolled in the study within the first 6 months.

Late Recurrence

Patients who develop a 'late recurrence' after platinum/paclitaxel pretreatment can be successfully treated with platinum once more. The study of carboplatin vs. carboplatin/paclitaxel originally planned by the AGO Ovarian Carcinoma Group could not be continued because of lack of acceptance by the patients (see above). Instead, a new study has been initiated comparing carboplatin as single-agent therapy with a combination of carboplatin and gemcitabine. However, the study is in the initial phase so that at the moment not even preliminary results can be presented.