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BRIEF ARTICLE

Platinum-resistant ovarian cancer: Prematurely stopped phase Ⅱ Austrian AGO chemotherapy studies

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Abstract

AIM: To report the results of two phase Ⅱ studies of chemotherapy in patients with platinum-resistant and platinum-refractory ovarian cancer and discuss the current status of systemic therapy in this disease.

METHODS: Two subsequent Austrian Arbeitsgemeinschaft für Gynäkologische Onkologie (AGO) phase Ⅱ studies have been carried out. Patients either had platinum-refractory or platinum-resistant disease, i.e., disease progression during first line platinum-based therapy or recurrence within 6 mo following the last platinum-containing chemotherapy, respectively. In the first study, 6 cycles of irinotecan at 55 mg/m^2 and docetaxel 25 mg/m^2 were both administered on days 1, 8 and 15 of a 4 wk cycle. In the second phase Ⅱ study, either non-pegylated (PEG) liposomal doxorubicin (L-DXR) 60 mg/m^2 monotherapy on day 1 and PEG filgrastim on day 2 (arm A) or L-DXR at 50 mg/m^2 and gemcitabine (GEM) at 650 mg/m^2 on day 1 and GEM on day 8 (arm B) were administered every 4 wk. Patients in arm B received prophylactic filgrastim 5 μg/kg per day from days 3 to 6 and from days 9 to 12, respectively.

RESULTS: Response rates in studies were 14% and 17%, respectively. The progression-free survival was less than 3 mo. Diarrhea was most prevalent in patients treated with irinotecan + docetaxel, while stomatitis/mucositis occurred in a quarter of patients treated with L-DXR +/- GEM + granulocyte colony stimulating factor, respectively. Following treatment with the latter regimen, a total of 11 serious adverse events were recorded among the 12 patients included. The rate of remissions of the regimens used in these two Austrian AGO studies was low and their toxicity significant. Due to their low therapeutic index, neither of these regimens can be recommended in this heavily pretreated patient population with platinum-resistant ovarian cancer exhibiting a high tumor-associated symptom burden.

CONCLUSION: The two reported phase Ⅱ studies of the Austrian AGO in platinum-resistant disease had to be terminated prematurely due to a low therapeutic index. Treatment of this disease remains a clinical dilemma. Bevacizumab seems to be active at this late-

stage disease but may be associated with significant bowel toxicity.

Key words: Platinum-resistance; Ovarian cancer; Chemotherapy; Gemcitabine; Non-pegylated liposomal doxorubicin; Irinotecan; Docetaxel

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INTRODUCTON

Ovarian cancer carries the highest mortality among all gynecological malignancies. In this disease, after an initial response to platinum and a taxane, resistance development is a significant problem. At this stage of disease, patients usually suffer from significant tumor-related symptoms and chemotherapy is only moderately active. The median survival lies between 6 and 11 mo[1,2].

In platinum-resistant ovarian cancer, monotherapy with pegylated (PEG)-liposomal doxorubicin (L-DXR), weekly paclitaxel, topotecan and gemcitabine (GEM) are the most commonly used agents[3,4]. There is an urgent need for more effective therapies able to induce a remission and thus leading to effective palliation.

Since 2005, the Austrian Arbeitsgemeinschaft für Gynäkologische Onkologie (AGO) has initiated three subsequent studies which investigated the use of combination regimens in platinum-refractory and platinum-resistant ovarian cancer. One study of topotecan and γ-interferon will be published elsewhere.

The results of the other two phase Ⅱ studies are reported here. The aim was to define the response rates, the progression-free survival and the toxicity profiles. The authors also discuss the current status of systemic therapy in platinum-resistant disease.

MATERIALS AND METHODS

Two subsequent Austrian AGO phase Ⅱ studies were carried out between 2005 and 2011 (Table 1). All patients either had platinum-refractory or platinum-resistant disease, i.e., disease progression during first-line platinum-taxane therapy or recurrence within 6 mo following the last platinum-containing chemotherapy, respectively. Patients were treated at the Departments of Obstetrics and Gynecology of the Medical Universities of Graz, Innsbruck and Vienna, as well as at the Departments of Gynecology of the Hospitals Barmherzige Schwestern in Linz, Ried and the Hospital Barmherzige Brüder, Graz and the Departments of Obstetrics and Gynecology, Wels, Neunkirchen and Kufstein.

Table 1 Patient characteristics and efficacy results of weekly irinotecan + docetaxel and non-pegylated liposomal doxorubicin +/- gemcitabine + G-CSF in the 27 patients with platinum-resistant or platinum-refractory ovarian cancer *n* (%)

	Weekly Irinotecan + docetaxel	Liposomal doxorubicin +/- gemcitabine + G-CSF
Included/planned	15/45	12/80
Years of study inclusion	2005-2006	2008-2011
Age (yr), median (range)	56 (33-77)	65 (46-77)
Previous regimens, median (range)	1.9 (1-4)	1.6 (1-3)
Platinum-refractory disease	8 (53)	1 (8)
Platinum-resistant disease	7 (47)	11 (92)
No. of previous chemotherapy regimens		
1	8 (53)	1 (8)
2	3 (13)	10 (83)
3	2 (13)	1 (8)
4	2 (13)	0 (0)
Previous taxanes	12 (80)	12 (100)
Complete response	1 (7)	0 (0)
Partial response	1 (7)	2 (17)
Stable disease	2 (13)	2 (17)
Progressive disease	11 (73)	8 (67)
Progression-free survival (mo), median (range)	2.8 (2.0-3.6)	2.1 (1.0-9.0)
Overall survival from study inclusion (mo), median (range)	10 (7.8-12.2)	10 (2.1-44.2)

Both studies were approved by the institutional Ethics Committees. For inclusion, patients had to sign an informed consent, to have no secondary cancer, no previous radiotherapy, no active infections, an adequate bone marrow function and liver parameters, as well as a serum creatinine of less than 2.5 × normal.

Progression was defined as the occurrence of new measurable disease by computed tomography scan and/or by chest X-ray.

In the first study, treatment consisted of 6 cycles of irinotecan at 55 mg/m^2 and docetaxel 25 mg/m^2, both administered on days 1, 8 and 15 of a 4 wk cycle.

In the second randomized phase Ⅱ study, either non-PEG L-DXR 60 mg/m^2 monotherapy on day 1 and PEG filgrastim on day 2 (arm A) or L-DXR at 50 mg/m^2 and GEM at 650 mg/m^2 on day 1 and GEM on day 8 (arm B) were administered every 4 wk, respectively. Patients in arm B received prophylactic filgrastim 5 μg/kg per day from days 3 to 6 and from days 9 to 12, respectively.

Pretreatment patient characteristics are shown in Table 1.

RESULTS

Treatment efficacy

Efficacy results of the two phase Ⅱ studies with irino-

Table 2 Worst grade 3 and 4 toxicities (National Cancer Institute-common toxicity criteria) per patient with platinum-resistant or platinum-refractory ovarian cancer undergoing weekly irinotecan + docetaxel and non-pegylated liposomal doxorubicin +/- gemcitabine + G-CSF *n* (%)

Grade 3 and 4 toxicity	Weekly irinotecan + docetaxel	Liposomal doxorubicin +/- gemcitabine + G-CSF
Patients	15 (100)	12 (100)
Neutropenia grade 4	0 (0)	2 (17)
Neutropenia grade 3	2 (13)	4 (33)
Febrile neutropenia grade 4	1 (7)	2 (17)
Leucopenia grade 3	2 (13)	3 (25)
Leucopenia grade 4	0 (0)	1 (8)
Thrombocytopenia grade 4	0 (0)	2 (17)
Nausea grade 3	0 (0)	1 (7)
Stomatitis/mucositis grade 3	0 (0)	3 (25)
Diarrhea grade 3	4 (27)	0 (0)
Diarrhea grade 4	1 (7)	0 (0)
Infection grade 3	0 (0)	2 (17)
Fatigue grade 3	1 (7)	2 (17)
Pain grade 3	1 (7)	2 (17)
Thromboembolism grade 3	2 (13)	1 (7)
Weight gain grade 3	1 (7)	0 (0)

Table 3 Serious adverse events observed in the two Austrian Arbeitsgemeinschaft für Gynäkologische Onkologie phase Ⅱ studies using irinotecan + docetaxel or liposomal doxorubicin +/- gemcitabine + G-CSF in patients with platinum-resistant and platinum-refractory ovarian cancer *n* (%)

Type of SAE	Weekly irinotecan + docetaxel (*n* = 15)	Liposomal doxorubicin +/- gemcitabine (*n* = 12)
Subileus and fatigue	0	3 (25)
Uncontrollable vomiting and fever	0	2 (17)
Febrile neutropenia	0	1 (8)
Pulmonary embolism/deep pelvic vein thrombosis	2 (13)	1 (8)
Pneumonia	0	1 (8)
Significant pleural effusion	0	1 (8)
Mucositis/diarrhea	1 (7)	1 (8)
Generalized edema	0	1 (8)
Total number of SAE	3 (20)	11 (91)

SAE: Serious adverse events.

tecan + docetaxel and L-DXR +/- GEM + G-CSF are shown in Table 1. In brief, the majority had platinum-resistant disease and the response rates were 14% and 17%, respectively. The median progression-free survival was less than 3 mo and the overall survival 10 mo, respectively.

Toxicity

Grade 3 and 4 toxicities are outlined in Table 2 and serious adverse events (SAE) in Table 3, respectively. Diarrhea was most prevalent in patients treated with irinotecan + docetaxel, while stomatitis/mucositis occurred in a quarter of patients treated with L-DXR +/- GEM, respectively. Table 3 shows the SAE observed in both studies. Following treatment with L-DXR +/- GEM, a total of 11 SAE occurred among the 12 patients included.

Both studies were stopped prematurely based on a decision of the AGO steering committee. It was felt that the harms for the patients in terms of toxicity were greater than its potential use.

Quality of life was examined in both phase Ⅱ studies. However, the early termination of both studies prohibited meaningful analyses.

Table 4 shows commonly used systemic therapy regimens in patients with platinum-resistant ovarian cancer.

DISCUSSION

Both phase Ⅱ AGO studies in patients with platinum-resistant ovarian cancer reported here exerted only a low therapeutic index. The rate of remissions was low and the toxicity significant. In the second phase Ⅱ study, G-CSF was prophylactically administered. However, its administration did not increase the tolerability of these regimens (Tables 2 and 3). Both studies were terminated prematurely.

In platinum-resistant or platinum-refractory ovarian cancer, treatment options are limited. Most patients die from the disease within 1 year[1,2] (Table 2). In this late stage disease, not only grade 3 or 4 toxicities but even the combination of several grade 2 toxicities, such as stomatitis, nausea, vomiting or fatigue, can deteriorate the patient´s performance status and motivation. Thus, the combination of cancer-related symptoms and toxicities is particularly critical when two-drug regimens are used.

There are only a limited number of studies published in platinum-resistant ovarian cancer, including one from our group in which combination therapy was found to be significantly effective on one hand and acceptably tolerated on the other[5]. Canfosfamide and PEG L-DXR showed a better therapeutic index than PEG L-DXR alone in one randomized phase Ⅱ study. Palmoplantar erythrodysesthesia and stomatitis were less pronounced in the combination arm[6].

Recently, single agent NKTR-102, a topoisomerase I-inhibitor polymer conjugate, demonstrated a response in 20% of patients after failure on PEG L-DXR[7].

In platinum-resistant disease, the induction of a remission is particularly necessary to reduce cancer-related symptoms, including subileus, abdominal distension and dyspnea[2].

Targeted therapies

In combination with tamoxifen, targeted therapy such as gefitinib, a tyrosin kinase inhibitor of the epidermal growth factor receptor, has shown only modest efficacy in platinum-resistant or platinum-refractory ovarian cancer. This regimen was associated with significant drug-related adverse events, including diarrhea and acne-like rash[8].

Bevacizumab is an antibody against vascular endo-

Table 4 Commonly used systemic therapy regimens in patients with platinum-resistant or platinum-refractory ovarian cancer

Chemotherapy regimen	Dose	Interval	Remarks
PEG-liposomal doxorubicin	40-45 mg/m^2 per day iv	day 1 every 4 wk	No alopecia, non-significant nausea/emesis, minor myelosuppression, significant hand-foot syndrome in 10% to 20%, respectively
Paclitaxel weekly	80 mg/m^2 per day iv (1-h-infusion)	Once weekly for three doses followed by 2 wk rest	Complete alopecia, no peroral premedication with dexamethasone necessary, minor myelosuppression, less neurotoxicity compared with 3-weekly paclitaxel
Gemicitabine	1000-1250 mg/m^2 per day iv	Days 1 + 8 every 3 wk	No alopecia, minor nausea/emesis, significant myelosuppression
Topotecan weekly	4 mg/m^2 per day iv	Days 1, 8, 15 every 4 wk	Moderate myelosuppression, rarely emesis/nausea, rarely significant alopecia
Bevacizumab	15 mg/kg per day iv	Day 1 every 3 wk	Significant hypertension, gastrointestinal perforations in up to 11%
Tamoxifen	20 mg/d	Daily	Response rate around 10%, mild toxicity

iv: Intravenously; PEG: Pegylated.

thelial growth factor. In a phase Ⅱ study, bevacizumab monotherapy resulted in a remarkable response rate in 16% in patients with platinum-resistant disease. However, gastrointestinal perforation occurred in as many as 11% of patients[9]. The prevalence of the latter complication was also high in a retrospective study which included heavily pretreated patients who had received a median of seven prior regimens. Bevacizumab was combined with cyclophosphamide, 5-fluoruracil, docetaxel or PEG L-DXR/GEM. The 35% response rate was encouraging[10].

In one phase Ⅱ study of bevacizumab and weekly topotecan, partial responses were seen in 24% and disease stabilization in another 36% of patients[11]. Although the response rate again was encouraging (46%), the combination of weekly PEG L-DXR and bevacizumab exerted significant toxicity, mainly including hand-foot syndrome and mucositis[12].

Thus, the ideal combination partner of bevacizumab remains to be defined. The Aurelia study is currently addressing this question (ClinicalTrials.gov identifier: NCT00976911).

Whether pertuzumab combined with GEM[13] or other regimens may expand the current armamentarium against platinum-resistant ovarian cancer needs confirmation in larger studies.

Antihormonal therapies

Antihormonal treatments such as tamoxifen or gonadotropin-releasing hormones have revealed remission rates in only about 10% of patients but, in addition, disease stabilizations in about one third of women treated[14,15]. Antihormonal effects do not seem to depend on the existence of hormone receptors of the tumor. One advantage of tamoxifen and similar agents is its mild toxicity.

In conclusion, a low therapeutic index was observed in both Austrian AGO phase Ⅱ studies using irinotecan + docetaxel and non-PEG doxorubicin +/- GEM + G-CSF, respectively. Both regimens cannot be recommended in platinum-resistant disease which remains a clinical dilemma. Bevacizumab seems to be active at this late-stage disease but may be associated with significant bowel toxicity. Studies defining combination partners for this monoclonal antibody are underway. Antihormonal therapy such as tamoxifen also has a place in the treatment of platinum-resistant and platinum-refractory ovarian cancer.

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COMMENTS

Background

The development of platinum resistance in ovarian cancer is a major clinical problem. New effective chemotherapy regimens are urgently needed.

Research frontiers

In the situation of non platinum-sensitive recurrent ovarian cancer, patients suffer from significant tumor-related symptoms and chemotherapy is only moderately active. The median survival lies between 6 and 11 mo.

Innovations and breakthroughs

In the heavily pretreated population with platinum-resistant ovarian cancer, two phase Ⅱ studies were unable to establish a new combination regimen with a favorable therapeutic index.

Applications

None of the combination regimens investigated by the Austrian Arbeitsgemeinschaft für Gynäkologische Onkologie can be recommended.

Terminology

Platinum-refractory and platinum-resistant recurrence: Patients either have disease progression during first-line platinum-taxane therapy or recurrence within 6 mo following the last platinum-containing chemotherapy, respectively.

Peer review

This is an interesting article in this field. The randomized trial compares two treatment regimens which are different for two variables.

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