

Survival outcomes in patients with recurrent ovarian cancer who were treated with chemoresistance assay-guided chemotherapy

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OBJECTIVE: The purpose of this study was to determine the outcome of patients with recurrent ovarian carcinoma after extreme drug resistance assay-directed therapy.

STUDY DESIGN: Fifty women who were treated with chemotherapy based on extreme drug resistance assay guidance were compared with 50 well-balanced control subjects who were treated empirically.

RESULTS: In the platinum-sensitive group, patients with extreme drug resistance-directed therapy had an overall response rate of 65% compared with 35% in the patients who were treated empirically ($P = .02$). The overall and progression-free median survival were 38 and 15 months in the extreme drug resistance assay group compared with 21 and 7 months in the control group, respectively ($P = .005$, overall; $P = .0002$, progression free). In the platinum-resistant group, there was no improved outcome in the patients who underwent assay-guided therapy. In multivariate analysis, platinum-sensitive disease, extreme drug resistance-guided therapy and early stage of disease were independent predictors for improved survival.

CONCLUSION: In this retrospective analysis, our results indicate an improved outcome in patients with recurrent ovarian carcinoma who have platinum sensitive disease and who underwent extreme drug resistance-directed chemotherapy. Randomized, prospective, controlled trials are needed. (*Am J Obstet Gynecol* 2003;189:1301-7.)

Key words: Chemoresistance, assay, chemotherapy, recurrent ovarian cancer

As the most lethal gynecologic malignancy in the United States, ovarian cancer causes approximately 14,500 deaths annually. With an annual incidence of 26,600 cases, the lifetime risk of ovarian carcinoma is 1 in 70, and the lifetime death rate is 1 in 100.¹ Cisplatin-based chemotherapy has significantly improved the duration of survival of patients with advanced ovarian cancer; its impact on cure is less certain. Although primary ovarian carcinomas initially respond to platinum-based chemotherapy in up to 80% of women with advanced disease, responses typically are incomplete, and most such patients will relapse.²⁻⁴ Accordingly, despite good initial responses to chemotherapy, 75% of women with stage III or IV disease die of complications associated with disease

progression.⁵ Given the high recurrence rate and poor long-term survival of women with advanced ovarian cancer, there is a strong impetus to investigate new technologies that might permit more effective treatment of women who have recurrence.

Patients with ovarian cancer who have relapse are characterized often as having platinum-resistant (PR) disease or platinum-sensitive (PS) disease, depending on the interval to progression after initial platinum-based chemotherapy. Patients whose condition progresses after a treatment-free interval of ≤ 6 months are typically considered to have PR disease, whereas patients who have relapse after a treatment-free interval of >6 months are considered to have PS disease.⁶ Patients with PS disease generally have a more favorable prognosis with a better response to second-line chemotherapy than do patients with PR disease.^{5,7}

The best strategy for the selection of second-line therapy after relapse has not been defined. Unfortunately, when second-line therapy is ineffective, patients are subjected to substantial costs and a risk of drug-induced toxicities without measurable benefit. Furthermore, ineffective second-line chemotherapy can induce cross-resistance to subsequent agents that might have been effective, thus decreasing the possibility of a clinical response.⁸⁻¹⁰

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Received for publication December 17, 2002; revised February 26, 2003; accepted May 14, 2003.

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0002-9378/2003 \$30.00 + 0

doi:10.1067/S0002-9378(03)00629-X

Table I. Characteristics of patients with PS and with PR recurrent ovarian cancer

	PS			PR		
	w/EDR	Control	P value	w/EDR	Control	P value
No. of patients	31	31		19	19	
Median age (range)	57 (19-77)	54 (33-85)		55 (42-72)	54 (33-70)	
Race			.53			.35
White	29	27		16	18	
African American	0	1		1	1	
Asian	2	3		2	0	
Stage			.45			.77
IC	6	4		1	1	
IIA	1	1		0	0	
IIC	0	2		0	0	
IIIA	0	2		0	0	
IIIB	0	0		1	0	
IIIC	22	21		13	13	
IV	2	1		4	5	
Tumor histologic grade			.25			.86
Grade 1	4	2		2	3	
Grade 2	8	14		5	4	
Grade 3	19	15		12	12	
Cell type			.37			.34
Serous	20	19		13	15	
Endometrioid	9	7		4	4	
Mucinous	0	2		0	0	
Clear Cell	2	3		2	0	
Optimal debulking (<2 cm residual disease)	28	27	.69	10	11	.74
Secondary cytoreductive surgery	28	28		—	—	
Reassessment laparotomies	11	13		16	17	

PS, Platinum-sensitive; PR, platinum-resistant; EDR, extreme drug assay.

In vitro extreme drug resistance (EDR) assays have received considerable attention over the last 20 years.¹¹ Although generally viewed as unreliable in identifying agents that are likely to be effective, their ability to identify agents with <1% likelihood of activity can permit the physician to avoid administering toxic agents that do not provide a realistic likelihood of therapeutic benefit.⁸⁻¹⁰ Nevertheless, there are no published reports that demonstrate an improved survival in patients who have a relapse of ovarian cancer who underwent chemotherapy selected on the basis of in vitro drug testing.¹²

We proposed to determine the disease-free and overall survival and response rates among patients with recurrent ovarian carcinoma (ROC) after EDR assay-directed therapy compared with those patients with no assay data. Furthermore, we divided our study population on the basis of their platinum sensitivity or resistance to determine whether the EDR assay is useful in guiding treatment of either subset of patients.

Material and methods

EDR assay. A viable tumor specimen that weighed 1 to 5 g was excised by the surgeon and submitted overnight in transport media to Oncotech, Inc (Irvine, Calif). The tritiated thymidine uptake drug resistance assay procedures were performed according to previously published protocols.^{13,14}

Classification of resistance. The degree of in vitro drug resistance to tumor specimens was stratified among three categories. Low drug resistance (LDR) was said to exist when the assay result after exposure to a given drug was greater than the median percent cell inhibition; EDR existed when the assay result was less than the median percent cell inhibition minus 1 SD, and intermediate drug resistance existed when the assay result was between LDR and EDR.

Patients and treatment. Between December 1993 and August 2002, we evaluated 100 patients with recurrent ovarian cancer at first relapse at University of California, Irvine and Long Beach Memorial Medical Center. Fifty consecutive patients who underwent chemotherapy on the basis of EDR assay guidance (EDR group) were compared with 50 well-balanced control subjects (control group) who received chemotherapy that was chosen without assay information. Both groups were comparable with respect to age, race, stage of disease, tumor grade, cell type, extent of surgical debulking, and the number of secondary cytoreductive operations for recurrent disease (Table I). For primary chemotherapy, all patients had received either a platinum-paclitaxel or platinum-cyclophosphamide regimen that was begun within 28 days of primary cytoreductive surgery. A median of six cycles of primary chemotherapy had been administered to both groups. We divided our patient population into PR and PS

Table II. Comparison of second-line chemotherapeutic agents used in patients with PS and PR disease

	PS		PR	
	w/EDR	Control	w/EDR	Control
No. of patients	31	31	19	19
Single agent				
Carboplatin	4	0	1	0
Cisplatin	1	3	5	1
Topotecan	3	4	1	4
Paclitaxel	6	4	5	2
Gemcitabine	2	0	0	0
Liposomal doxorubicin	1	1	0	4
Etoposide	0	0	1	0
Hexamethylmelamine	0	0	0	3
Drug combinations				
Carboplatin + paclitaxel	7	13	1	0
Cisplatin + paclitaxel	3	0	2	0
Cisplatin + gemcitabine	3	0	0	0
Cisplatin + cyclophosphamide	1	2	3	1
Carboplatin + cyclophosphamide	0	0	0	2
Cisplatin + etoposide	0	1	0	0
Cisplatin + bleomycin	0	0	0	1
Carboplatin + doxorubicin	0	0	0	1
Carboplatin + paclitaxel + liposomal doxorubicin	0	1	0	0
Carboplatin + topotecan + hexamethylmelamine	0	1	0	0
Cisplatin + doxorubicin + cyclophosphamide	0	1	0	0

PS, Platinum-sensitive; PR, platinum-resistant; EDR, extreme drug resistance assay.

groups to compare, with the control group, the effects of EDR-directed chemotherapy on clinically resistant and sensitive tumors. We calculated the differences in progression-free survival (PFS) between the EDR and control groups from the completion of initial chemotherapy to first recurrence. In patients with PS disease, the EDR group had a median PFS of 34 months versus 23 months in the control group ($P = .12$). In patients with PR disease, the median PFS to first recurrence was 2 months in the EDR group and 2 months in the control group ($P = .51$).

The decision to perform EDR assay was determined by the volume of disease found during surgery and the surgeon's preference. Specimens used for EDR assays were obtained in the following manner: 28 specimens were collected at secondary cytoreductive operations, 16 specimens were collected at reassessment laparotomies (ie, second-look laparotomies), 4 specimens were collected from needle aspiration of ascites or pleural fluid, and 2 specimens were collected from inguinal lymph nodes with metastases. All 28 specimens that were collected from cytoreductive surgeries and all 16 specimens that were obtained from reassessment laparotomies were from women with PS and PR disease, respectively. Specimens were removed from omental deposits, intestinal serosa and mesentery, subdiaphragmatic surfaces, inguinal lymph nodes, peritoneal surfaces, and vagina. When solid tumor was not available for assay, pleural and peritoneal fluids were used. The tumor or cytologic specimens typically were tested with several drugs in the assays that included carboplatin, paclitaxel, topotecan, liposomal doxorubicin, etoposide, gemcitabine,

hexamethylmelamine, cyclophosphamide, and cisplatin as single agents and gemcitabine/cisplatin in combination. All 50 patients in the EDR group were treated with the chemotherapeutic regimen that predicted a LDR according to the chemoresistance assay results (Table II). When >1 agent was found to have a LDR, the physician selected the drug or drug combinations to be used on the basis of the patients' toxicity profile. Because there is no evidence that demonstrates a benefit of the use of combination chemotherapy in the treatment of ROC, most patients were treated with single-agent chemotherapy. Data were collected from hospital charts, clinic follow-up records, and tumor registry databases. Institutional review board approval from both institutions was obtained for the study.

Evaluation of response. Complete response to second-line chemotherapy was defined as the disappearance of all measurable disease for at least 4 weeks. Partial response was defined as a decrease of >50% in all measurable lesions for at least 4 weeks with no increase in any tumors or appearance of new lesions during this period. Progressive disease was defined as an increase of >50% in any measurable lesions or the appearance of ≥ 1 new lesions. Patients were classified as having stable disease if they did not qualify for complete and partial response or as having progressive disease. Responses were also evaluated by the measurement of serial CA 125 values. However, a decrease or normalization of serum CA 125 without a radiologic correlate or physical finding did not qualify a patient for complete or partial response. Patients were considered evaluable for response after a minimum of two cycles of

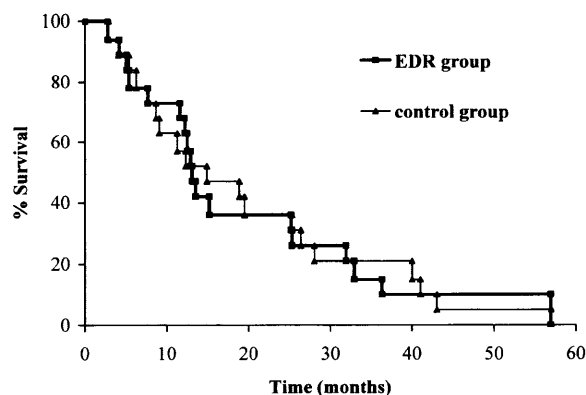


Fig 3. Kaplan-Meier analysis: overall survival of patients with PR disease.

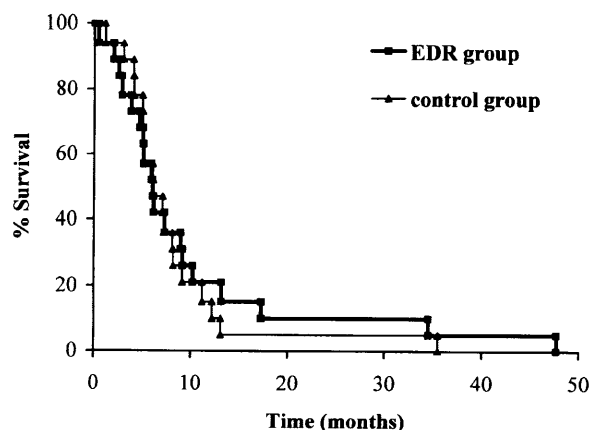


Fig 4. Kaplan-Meier analysis: PFS of patients with PR disease.

EDR group compared with 70% and 16% in the control group, respectively ($P = .005$, overall; $P = .0002$, progression-free; Table III, Figs 1 and 2). For patients with PS disease, the median length of follow-up from diagnosis was 63 months (range, 23-250 months).

Of the 38 patients with PR disease, 2 women had stage I disease, 27 women had stage III disease, and 9 women had stage IV disease (Table I). Of the 19 patients with PR disease in the EDR group, 13 women (68%) had single-agent and 6 women (32%) multiagent chemotherapy versus 14 women (74%) who were given single-agent and 5 women (26%) who were given multiagent chemotherapy in the control group ($P = .72$, Table II). Women with PR tumors who underwent EDR-directed therapy had an overall response rate of 21% compared with 16% in the control group ($P = .68$), with two complete (10.5%) and two partial (10.5%) responses in the EDR group versus two complete (10.5%) and one partial (5.5%) response in the control group. The overall and progression-free median survivals were 13 and 5 months in the EDR group compared with 12 and 6 months in the control group, respectively. Furthermore, the 1-year overall and PFS rates were 68% and 16% in the EDR group compared with 58% and 16% in the control group, respectively ($P = .88$, overall; $P = .90$, progression-free; Table III, Figs 3 and 4). For patients with PR disease, the median length of follow-up from diagnosis was 21 months (range, 6-65 months).

Multivariate analysis was performed to identify independent prognostic factors that were responsible for survival. Our results found three independent factors that were associated with decreased overall survival: PR versus PS disease (hazard ratio, 1.77; 95% CI, 1.09-2.87), choice of second-line chemotherapy based on clinical judgment alone versus EDR guidance in PS disease (hazard ratio, 1.63; 95% CI, 1.02-2.62), and advanced stage of disease (hazard ratio, 1.91; 95% CI, 1.17-3.14).

There were no significant differences between the adverse effects from chemotherapy between the EDR-

directed regimens compared with control regimens in both PS and PR groups. Six percent of the patients in the EDR group had grade III and IV hematologic toxicity compared with 4% in the control group. Neurotoxicity was found in only two patients who were treated in the EDR group. Severe nausea and vomiting occurred in 6% of women in the EDR group compared with 4% in the control group. One patient from both the assay and control group experienced a hypersensitivity reaction. One woman from the EDR group had severe oral mucositis.

Comment

Although many previous reports have demonstrated a positive correlation between in vitro drug testing and overall clinical response in patients with primary ovarian cancer, none have shown a significant improvement in overall survival.¹⁴⁻²¹ Similarly, the role of in vitro drug testing in ROC has not been well defined because of a lack of convincing data which show that the information it provides improves overall survival.

In this retrospective analysis, our results showed an improved response rate and duration of progression-free and overall survival in patients with PS disease who underwent second-line chemotherapy that was guided by EDR assays compared with those who were treated by clinical judgment alone. This suggests that there may be a well-defined patient group for whom EDR testing might be of benefit. Because patients with PS ovarian cancers typically have a good response to second-line platinum-containing chemotherapy, we did not anticipate that EDR-directed chemotherapy could further enhance the response and survival in these patients. Nevertheless, we discovered that the 1-year PFS in the EDR group was 68% compared with 16% in the control group, a dramatic difference ($P = .0002$). Given the historically poor response rates of patients with ROC with PR tumors, we were particularly interested in the outcome of those patients

who underwent assay-guided therapy. We anticipated that the EDR-guided regimens might provide some clinical benefit in these women. On the basis of this analysis of a small number of patients, assay-directed therapy did not affect the outcome of women with PR recurrent ovarian cancer. Unfortunately, as demonstrated by many others, we found that few women with PR tumors were likely to benefit from second-line chemotherapy.

In our patient population, the EDR and control groups were comparable with respect to demographics, stage of disease, tumor grade, extent of surgical debulking, and type and number of cycles of primary chemotherapy. In addition, the overall recurrence and survival rates of the control group were comparable to those that are reported in the literature for women who undergo several lines of chemotherapy based on clinical judgment alone.^{2,3,22,23} Furthermore, we analyzed the differences in PFS from the completion of their initial therapy to first recurrence between the EDR and control groups. Previous studies have reported that the duration of the PFS from the completion of their therapy to first recurrence is an important prognostic indicator of response to subsequent therapy in ROC.²⁴ Eisenkop et al²⁵ found that survival was affected by the PFS of 6 to 12 months (median, 25 months) versus 13 to 36 months (median, 44 months) versus >36 months (median, 57 months) after the initial treatment ($P = .005$). Moreover, the authors did not report a survival difference in patients with PFS of 13 to 36 months. In our study, the patients with PS disease in the EDR group had a PFS of 34 months compared with 23 months in the control group ($P = .12$). Although these differences were not statistically significant, they might help to explain some of the differences in the response rates and survival statistics.

Because many of the operative reports did not describe in detail the volume of residual disease after secondary cytoreductive operations, we were not able to determine whether the benefits on survival that were demonstrated in the EDR group were associated with the amount of residual disease after secondary cytoreductive surgery. Intuitively, the patients in the EDR group confer a worse prognosis because patients with a higher volume of disease will have a greater likelihood of obtaining sufficient specimens for assay analysis. The benefits of secondary cytoreductive operation in ovarian cancer have not been demonstrated definitively in prospective randomized trials. However, studies have shown that secondary cytoreductive surgery does not benefit patients with short disease-free interval (eg, PR disease) but may benefit patients with long disease-free intervals, hence the high frequency of surgery in this platinum sensitive subgroup of patients. Most important, the number of patients who underwent cytoreductive surgeries in our study was not different between the EDR and control groups. Furthermore, there was no statistically significant differ-

ence between those women who received single versus multiagent chemotherapy in the EDR and control groups; however, there was a trend toward treating more patients with multiagent chemotherapy in the EDR group versus control group. This difference might have contributed to the observed differences in the trial. We acknowledge the lack of adequate power for hypothesis testing in this study. However, it was not our intent to design a study with a power analysis to determine a statistical difference between the EDR and control groups. This analysis was conducted for exploratory purposes with the intent of generating hypotheses worthy of further study.

The use of EDR assays to assist in making treatment decisions for women with ovarian cancers lies in its ability to exclude certain drugs with very low likelihood (<1%) of clinical activity rather than its ability to reliably predict agents that will show clinical activity. This occurs, in part, because in vitro assays cannot reproduce factors that exist in the patient that influence chemoresponsiveness such as variations in tumor vascularity, tumor growth fractions, immunologic factors, and drug metabolism.²⁶ Furthermore, the usefulness of these assays can be limited by the observation that the identification of chemoresistance to one drug among a panel of agents does not suggest that ≥ 1 of the remaining agents will be efficacious. In fact, at times, no agents show activity in many patients. Nevertheless, several studies have demonstrated that response rates to chemotherapy are improved when patients receive drugs to which their tumors were not resistant in vitro.^{14,26-29} In addition, Kurbacher et al,²¹ who used the results of ex vivo adenosine triphosphate luminescence assays to guide chemotherapy treatment of patients with ROC, found an improved response rate and PFS in women with PS tumors using assay-guided therapy compared with women who were treated empirically. The authors report an overall response rate of 64% in the assay group with a PFS of 13 months compared with 37% and 5 months in the control group, respectively ($P = .04$, response; $P = .003$, PFS). Because of the short-term follow-up and limited number of patients, the authors were not able to demonstrate an overall survival benefit using assay-directed therapy.

Even in the absence of clinical trials, it is obvious that there is a therapeutic disadvantage to the use of inactive drugs in patients with cancers. This disadvantage is magnified in patients with ROC, where the response rate is expected to be much lower than with primary chemotherapy. Moreover, the "trial and error" approach is not only an ineffective use of health care resources³⁰ but can also lead to resistance to drugs that initially may have been effective. We believe that our data show that the use of information that is obtained from in vitro drug testing can provide the physician with chemotherapy treatment choices that offer a higher probability of patient benefit than that chosen on the basis of clinical judgment alone.

Clearly, the establishment of a definitive role for in vitro chemoresistance assays will depend on the analysis of randomized clinical trials.

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