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SHORT COMMUNICATION

A case of drug resistant clear cell ovarian cancer showing responsiveness to gemcitabine at first administration and at re-challenge

Gabriella Ferrandina · Francesco Legge · Valentina Mey · Sara Nannizzi · Simona Ricciardi · Marco Petrillo · Giacomo Corrado · Giovanni Scambia

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Abstract
Introduction Gemcitabine (2′,2′-difluorodeoxycytidine) (GEM) has been demonstrated to be active in the salvage setting of ovarian cancer (OC) patients.
Case report A 57-year-old woman, with a diagnosis of FIGO Stage IIIC clear cell OC, judged inoperable to optimal residual tumor, was administered neo-adjuvant chemotherapy with carboplatin/paclitaxel/topotecan, and cytoreduction. After 5 months the patient progressed, and pegylated liposomal doxorubicin was started with rapid progression. GEM (1,000 mg/m^2, d1,8,15, q28) was then started, and a complete clinical response was documented after seven cycles of treatment, and was maintained for 9 months; at progression fourth line carboplatin was attempted but 1 month after the last course of carboplatin, progression occurred, and the patient was re-challenged with GEM obtaining a partial response, of 6 months duration. Currently, the patient is still under treatment, without any complaints relative to her quality of life/specific symptoms.
Conclusion We described the case of a drug resistant clear cell ovarian cancer showing a selective susceptibility only to GEM at first administration and at re-challenge. Moreover, this case expressed a molecular profile very likely to support high tumour cell sensitivity to GEM.

Keywords Gemcitabine responsiveness · Molecular targets · Clear cell ovarian cancer

G. Ferrandina (✉) · F. Legge · M. Petrillo · G. Corrado
Gynecologic Oncology Unit, Catholic University of the Sacred Heart, L.go A. Gemelli 8, 00168 Rome, Italy
e-mail: gabriella.ferrandina@libero.it

G. Ferrandina · F. Legge · G. Scambia
Department of Oncology, Catholic University, Contrada Tappino, Campobasso, Italy

V. Mey · S. Nannizzi · S. Ricciardi
Division of Pharmacology and Chemotherapy, Department of Internal Medicine, University of Pisa, Pisa, Italy

Introduction

Recurrent ovarian cancer patients who experience recurrence after > 6 months from the completion of first-line treatment are considered platinum sensitive, and usually exhibit high rates of response to platinum re-challenge according to the duration of platinum-free interval [1]. On the other hand, in patients considered platinum resistant the rates of response to salvage treatment with many cytotoxic drugs remain low, and response is of short duration [1]. Among the drugs used in the salvage setting, much attention has been focused on gemcitabine (2′,2′-difluo rodeoxycytidine) (GEM), a synthetic nucleoside analogue demonstrated to achieve up to 17% response rate in the subgroup of platinum resistant ovarian cancer patients [2].

Tumor cellular susceptibility to GEM is the result of the complex interaction of several molecules such as the equilibrative nucleoside transporter-1 (hENT1), and the concentrative nucleoside transporter-1 (hCNT1) which carry the drug inside the cell, and deoxycytidine kinase (dCK), which phosphorylates and activates the pro-drug [3]. Moreover, the expression of the ribonucleotide reductase regulatory subunits M1 (RRM1) and M2 (RRM2), and the levels of GEM catabolic enzymes 5′nucleotidase (5′NT) and cytidine deaminase (CDA) are associated with chemosensitivity to GEM [3]. We report for the first time a case of recurrent ovarian cancer shown to be resistant to several cytotoxic drugs, but exhibiting a

selective high sensitivity to GEM not only at first administration, but at re-challenge. The investigation of the molecular targets playing a role in determining GEM susceptibility has been carried out.

Case report

A 57-year-old Caucasian woman, gravida 2, para 2, 11 years postmenopausal, was admitted to the Gynaecologic Oncology Unit of the Catholic University of Rome, complaining of abdominal distension. Imaging studies revealed a large abdominal mass (maximum diameter = 20 cm) originating from the right ovary, ascites and multiple peritoneal nodules suggestive for diffuse carcinosis, and enlargement of pelvic lymph nodes. Ca125 serum levels were 4,625 IU/ml. Explorative laparotomy was performed documenting a large ovarian mass adherent to prevesical and prerectal peritoneum, diffuse abdominal carcinosis, agglutinated bowel/mesentery, and omental cake. The patient was judged not susceptible to be optimally cytoreduced, and only removal of the adnexal mass and radical omentectomy, as well as multiple peritoneal biopsies were performed. Definitive histopathology reported a clear cell histology. Immunohistochemistry documented a strong immunoreaction for p53 protein in 100% of tumor cells, while positive Ki67 expression was found in 30% of tumor cells. Immunostaining was negative for HER2/neu, cyclin D1, and bcl-2 protein. The case was classified as FIGO stage IIIC, and chemotherapy was started with the combination carboplatin (5 AUC), paclitaxel (175 mg/m^2), and topotecan (1 mg/m^2, d1–3), on a three weekly basis. After 6 cycles, total body CT scan documented only a 15% reduction of the sum of the longest diameters of the target lesions (no change of disease), with residual disease (diameter up to 3 cm) in the abdomen. Moreover, CA125 levels dropped to 300 IU/ml. Interval debulking surgery was attempted and total hysterectomy, removal of the left ovarian mass, and cytoreduction of intra-abdominal nodules were performed, leaving a residual tumor of 0.5 cm at ileum and its mesentery. Additional 4 cycles of chemotherapy with carboplatin–paclitaxel combination were administered. After 5 months CT scan documented progression of disease, and the increase of Ca125 levels up to 905 U/ml. Salvage chemotherapy with pegylated liposomal doxorubicin (40 mg/m^2, q21) was started. Disease progression, as assessed by CT scan, was shown after 3 cycles, and gemcitabine (GEM) (1,000 mg/m^2, d1,8,15, q28) (dose intensity = 750 mg/m^2/week) was started. After 7 cycles CT scan documented a complete clinical response which lasted 9 months; moreover, CA125 levels returned to normal values. On further progression of disease, as assessed by CT scan, chemotherapy with carboplatin (5 AUC, q28) for 8 cycles was attempted leading to stabilization of disease. One month later, further progression was documented and the patient was triaged to re-challenge with GEM: a partial response was obtained after 6 cycles of chemotherapy; Ca125 levels dropped from 650 IU/ml to normal levels after 5 cycles. The 15-day GEM dose was not administered because of the haematological toxicity; therefore, dose intensity was 500 mg/m^2/week. The duration of response is currently 6 months, and the patient is still under treatment, showing an ECOG performance status of 1, without any complaints relative to her quality of life, or to specific symptoms. The evaluation of biological markers was performed by quantitative PCR analysis, as previously described [4], in tumor tissue specimens obtained at time of first surgery from this case and, as a reference, from additional eight advanced ovarian carcinomas. In this series, the data about response to GEM was available in five patients: the current case (responsive) and four cases who showed no response to GEM. As summarized in Table 1, our case

Table 1 Distribution of hENT1, hCNT1,dCK, RRM1, RRM2, 5′NT, and CDA in the whole series and in the current case (No.9)

	Histo	Stage	hENT1	hCNT1	dCK	RRM1	RRM2	5′NT	CDA	RATIO	Response to GEM
1	Serous	IIIC	0.79	0.60	0.80	0.85	0.77	0.85	0.71	0.98	No
2	Serous	IIIB	0.78	0.56	0.79	0.85	0.81	0.83	0.68	0.89	NA
3	Serous	IIIC	0.86	0.69	0.87	0.88	0.82	0.92	0.74	1.02	NA
4	Serous	IIIC	0.88	0.72	0.83	0.90	0.89	0.94	0.79	0.91	NA
5	Serous	IIIC	0.80	0.67	0.80	0.87	0.82	0.85	0.69	0.89	No
6	Serous	IV	0.80	0.65	0.82	0.87	0.82	0.87	0.76	0.92	No
7	Edometrioid	IIC	0.80	0.60	0.73	0.78	0.70	0.80	0.68	0.74	No
8	Serous	IIIC	0.84	0.64	0.83	0.93	0.84	0.90	0.73	0.89	NA
9	Clear cell	IIIC	0.89	0.67	0.92	0.87	0.83	0.94	0.79	1.13	Yes

$\text{RATIO} = \frac{\text{hENT}\times\text{dCK}}{\text{RRM1}\times\text{RRM2}}$

NA not available

showed the highest values of hENT1 and dCK, while RRM1 and RRM2 were around the median value. We tried to combine the information deriving from all the parameters analyzed, by using the ratio between the product of hENT1 and dCK (the higher the expression, the higher the chance of GEM susceptibility), and the product of RRM1 and RRM2 (the lower the expression, the higher the chance of GEM susceptibility): our case ranked first in the series of ovarian carcinomas analyzed, thus expressing the molecular profile most likely, in principle, to be associated with GEM sensitivity, while the ratio was <1 in the four cases resistant to GEM.

Discussion

To our knowledge, this is the first description of an ovarian cancer patient showing a selective high responsiveness to GEM treatment, even when administered at re-challenge.

The high tumour sensitivity to GEM is particularly noteworthy considering the lack of clinical response to the other drugs, and seems to indicate that in the current case it does not simply reflect a generic drug sensitive phenotype: our case showed the highest levels of molecules involved in GEM transport and intracellular activation, respectively, and the molecular profile most likely to show a high sensitivity to GEM. In addition, when re-challenge with GEM was attempted, a clinical response was again observed, despite (1) the patient had already received four lines of treatment, and (2) GEM dose intensity had to be reduced to 500 mg/m^2/week because of haematological toxicity. The efficacy of GEM re-challenge seems to suggest that the role played by the molecular profile conceivably sustaining GEM responsiveness, is maintained over multiple and different chemotherapeutic treatments, thus leading to hypothesize that the transcription analysis of the panel of molecules affecting GEM activity could be reliably performed in the primary tumour, and maintain its ability to predict GEM responsiveness in the recurrent setting. Attempts should be made to investigate whether the selective sensitivity to GEM might reflect specific histologies, known to exhibit different gene expression signatures and different responsiveness to chemotherapy. Although our findings are too preliminary to draw any definitive conclusion, the data emphasize the potential clinical relevance of assessing the expression of genes/proteins determining GEM responsiveness in order to provide a more rational approach to the choice of the drug. This issue becomes even more relevant in the context of the salvage treatment of platinum resistant ovarian cancer patients, for which the usefulness of several lines of chemotherapy is debated, and who need to be spared unnecessary toxicity and/or impairment of quality of life, given their dismal prognosis.

References

1. Herzog TJ (2006) The current treatment of recurrent ovarian cancer. Curr Oncol Rep 8:448–454
2. D'Agostino G, Amant F, Berteloot P, Scambia G, Vergote I (2003) Phase II study of gemcitabine in recurrent platinum- and paclitaxel resistant ovarian cancer. Gynecol Oncol 88:266–269
3. Bergman AM, Pinedo HM, Peters GJ (2002) Determinants of resistance to 2′,2′ difluorodeoxycytidine (gemcitabine). Drug Resist Updat 5(1):19–33
4. Giovannetti E, Del Tacca M, Mey V, Funel N, Nannizzi S, Ricci S, Orlandini C, Boggi U, Campani D, Del Chiaro M, Iannopollo M, Bevilacqua G, Mosca F, Danesi R (2006) Transcription analysis of human equilibrative nucleoside transporter-1 predicts survival in pancreas cancer patients treated with gemcitabine. Cancer Res 66(7):3928–3935
5. Schwartz D, Kardia SLR, Shedden KA, Kuick R, Michailidis G, Taylor JMG, Misek DE, WuR, Zhai Y, Darrah DM, Reed H, Ellenson LH, Giordano TJ, Fearon ER, Hanash SM, Cho KR (2002) Gene expression in ovarian cancer reflects both morphology and biological behaviour, distinguishing clear cell from other poor prognosis ovarian carcinomas. Cancer Res 62:4722–4729