Brain Metastases in Relapsed Epithelial Ovarian Cancer after Chemotherapy with Pegylated Liposomal Doxorubicin

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Abstract. *Background: Brain metastases in epithelial ovarian cancer (EOC) occur rarely and are associated with a poor prognosis. No significant risk factors have been identified and no evidence-based treatment guidelines are currently available. Case Report: A 56-year-old EOC patient presented with seizure at the Emergency Department eleven days after completion of fourth-line chemotherapy with pegylated liposomal doxorubicin (PLD). A computed tomography (CT) scan revealed multiple metastases. The patient received radiotherapy with a total dose of 30.8 Gy and 8 cycles of paclitaxel resulting in stable disease. Based on the current literature, treatment options are discussed. Conclusion: Therapeutic options for brain metastases include radiation, systemic or intrathecal chemotherapy, surgery or a combination regime. Since the effectiveness of systemic chemotherapy remains controversial, current research focuses on developing new anticancer drugs that penetrate the blood-brain barrier in order to prevent and/or treat brain metastases.*

Epithelial ovarian cancer (EOC) is a rare disease with a lifetime risk of 1.4% . Nevertheless, it is the leading cause of death among all gynaecological malignancies worldwide due to the advanced stage of the disease at the time of initial diagnosis in most patients. Typical dissemination patterns of ovarian cancer are peritoneal seeding and lymphatic spread within the pelvic and paraaortic lymph nodes.

Brain metastases from ovarian cancer occur only rarely with an estimated incidence of 0.49-2.2% (1). A patient who developed multiple brain metastases shortly after fourth-line chemotherapy with pegylated liposomal doxorubicin (PLD), 73 months after primary diagnosis of epithelial ovarian cancer, International Federation of Gynecology and Obstetrics (FIGO) stage IIIc is presented. Additionally, an overview of the literature on brain metastases in ovarian cancer is given.

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Case Report

A 56-year-old woman with ovarian cancer initially diagnosed in May 2001, had undergone an explorative laparotomy with hysterectomy, salpingo-oophorectomy, systematic pelvic and paraaortic lymphadenectomy, infragastric omentectomy, peritonectomy of the urinary bladder and anterior resection of the rectum and sigmoid colon with end-to-end anastomosis. Optimal debulking had been achieved. Histological examination revealed a low grade (Grade 1) serous-papillary carcinoma, pT3b, pN1 (3/51). The gross and pathological findings correlated with a FIGO stage IIIc. Fourteen days post-operatively, chemotherapy with paclitaxel (175 mg/m^2) and carboplatin (AUC 5) (every 21 days) was initiated with the completion of 6 cycles.

A recurrence in the liver was found four years after the initial treatment (October 2005). Single-agent reinduction therapy with carboplatin AUC 4 (q21d) was instigated secondary to significantly elevated liver enzymes (aspartate aminotransferase, AST 284 U/l; alanine aminotransferase, ALT 464 U/l; alkaline phosphatase, AP 855 U/l; gamma-glutamyl-transferase, GGT 338 U/l). With normalization of liver enzymes (AST 35 U/l, ALT 27 U/l, AP 96 U/l, GGT 96 U/l), the patient was administered 2 cycles of carboplatin AUC 4 (d1) + gemcitabine 800 mg/m^2 (d1, 8; q21d) with completion in February 2006. No significant adverse events occurred during treatment.

Two months following the completion of second-line chemotherapy, new CT findings demonstrated a subhepatic mass measuring 22 mm. Additional indication of disease progression included increased cancer antigen CA-125 (256 U/ml) and the growth of multiple echogenic intrahepatic

lesions. Third-line chemotherapy was initiated with 8 cycles of topotecan 1.25 mg/m^2 (d1-5, q21d) (July through December 2006), however with no response (CT scan: increased peritoneal and hepatic tumour burden; CA-125: 1080 U/ml). Therefore, 6 cycles of PLD 40 mg/m^2 (q28d) were administered (January to June 2007).

At the end of June 2007, seventy-three months after the primary diagnosis and eleven days after the last cycle of fourth-line chemotherapy, the patient presented at the Emergency Department with seizure and associated loss of consciousness. The patient complained of word finding difficulties and blurred vision. The initial neurological examination was unremarkable apart from lower lip paraesthesia. Her previous history was negative for epileptic seizures or any neurological symptoms other than intermittent blurred vision during chemotherapy.

Due to the suspected diagnosis of brain metastases-induced seizure, a head CT scan was performed, which revealed multiple brain metastases, up to 2 cm in size, with isolated foci of vasogenic edema (see Figure 1). Three frontoparietal metastases with encompassing oedema, reduced central perfusion and possible haemorrhage near the left ventricle could also be detected (Figure 1). There were no signs of increased intracranial pressure.

A CT scan of the abdomen showed progressing liver metastases and newly developed ascites. At the time of admission, CA-125 was elevated at 594 U/ml. The general condition of the patient was good (ECOG=1).

Due to the progression of the disease under fourth-line chemotherapy with pegylated PLD, therapy with paclitaxel weekly 60 mg/m^2, was initiated.

In addition, prior to the chemotherapy whole brain radiotherapy (WBRT) was performed using two opposing radiation fields with 6 MV photons and a single dose of 2.8 Gy up to a total dose of 30.8 Gy. Fractionated stereotactic irradiation and radiosurgery were not considered due to the large number of metastases.

Symptomatic treatment to reduce vasogenic oedema included dexamethasone (initially 16 mg, then 3×8 mg/day) and furosemide (2×20 mg/day). Levetiracetam (500 mg/day) was also started due to the pathological EEG findings.

No subsequent epileptic seizures have been observed, though fatigue persisted, most likely due to the anti-epileptic treatment. A comparison abdominal CT scan after completion of 8 cycles of paclitaxel weekly revealed stable disease of the hepatic and peritoneal lesions with resolution of the ascites. CA-125 decreased to 401 U/ml after the treatment.

Discussion

Brain metastases are often seen in solid tumours such as lung cancer, breast cancer and malignant melanoma. However, they only rarely occur in patients with EOC. Brain autopsies of patients with ovarian cancer have shown metastatic lesions in only 0.9% of the cases, while several clinical studies have suggested an incidence between 0.49% and 2.2% (1, 2). In a recent meta-analysis, the average incidence of brain metastases in patients with EOC has been estimated to be 1.01% (1). A large retrospective study including 4456 patients over a study period of 40 years (1944-1984) showed that no EOC central nervous system metastases had been identified before 1968 (2). The possible increasement in the rate of brain metastases may have resulted from advances in the diagnostic tools and cancer management, which has led to a significant increase in overall survival (3). CT or MRI establishes the diagnosis of brain metastases, though high-quality, gadolinium-based contrast-enhanced MRI is considered to be the superior test and should be performed (5). Due the longer course of disease and the better options for abdominal tumor control (*e.g.* bowel sugery) it can be speculated that more patients experienced symptomatic brain metastases.

When EOC patients present with neurological symptoms, it is important to exclude brain metastasis. In a comprehensive review by Abrey and Dalmau studying 83 ovarian cancer patients requiring 121 neurology consultations, metastatic disease was found in 22% of the consultations (3). Common symptoms are altered mental status, neurological deficits, headaches, and seizures (3, 4). These symptoms can be temporary disguised by the prophylactic use of steroids for allergic reaction or the treatment of nausea and emesis. Another minority of patients suffer from leptomeninges carcinomatosis which has a very poor prognosis (13). Previous reviews of the literature have reported less than 20 cases of leptomeningeal metastases in ovarian carcinoma. Symptoms are more widespread in leptomeningeal carcinomatosis, including spinal and cranial nerve palsies.

Brain metastases, either single or multiple, occur after a median time of 21.5 months (range 0-126 months) following the initial diagnosis of EOC (4). In the majority of the cases, multiple lesions are found. Forty to sixty percent of the cases show disseminated recurrent disease, with the remaining cases showing the brain to be the only metastatic site (1, 6).

Generally, the prognosis of EOC patients and brain metastasis is very heterogeneous. Patients receiving only symptomatic treatments have a median survival of 2 months (range 0-15 months) while tumor targeting therapy, regardless of the modality employed, seems to improve median survival despite the fact that no randomized trials have been performed (6, 13, 14). According to Pectasides *et al.*, treatment including surgery, radiotherapy +/– chemotherapy shows advantages over other forms of treatment with a median survival of 20 months (range 1 – 57+ months) and 21.8 months (range 1 – 120+ months) respectively (1). The results of higher progression free survival and overall survival can be potentially influenced by

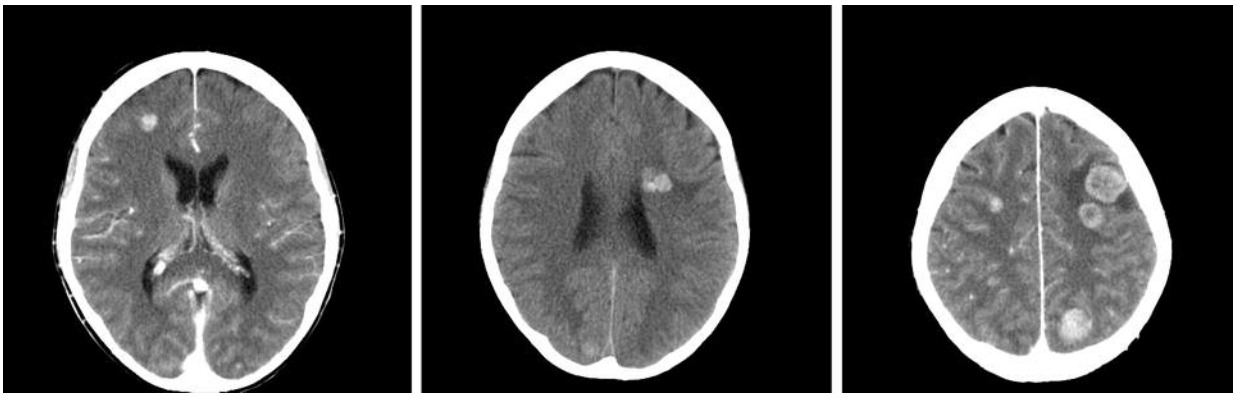

Figure 1. *A cranial CT revealing multiple ring enhancing lesions in the frontal, parietal and occipital regions. Their size ranged from a few millimeters up to 2 cm. Isolated metastases were surrounded by edema.*

the better general condition of the patients. This possible bias can be excluded only by conducting a prospective randomized study.

Various authors have suggested that patients with advanced disease (FIGO III and IV) and/or low grade tumor differentiation (grade 3 disease) are at higher risk for developing brain metastases (6, 15, 16), it is not yet feasible to define predictive factors for early detection due to the lack of data.

Currently, no standard treatment guidelines are available for EOC patients with brain metastases and must be individualized. Only single cases of long-term complete remissions after multidisciplinary therapeutic approaches comprising stereotactic surgery, radiation and chemotherapy have been reported.

Surgical resection, stereotactic radiosurgery, WBRT and chemotherapy are the current treatment options. Surgical resection is considered the best therapeutic approach and can be performed alone or in combination with chemotherapy and radiotherapy depending on the general condition of the patient and the specific tumor pattern. Surgical treatment modality including gamma-knife radio-surgery with WBRT has been shown to be superior to resection or WBRT alone (17).

The use of corticosteroids for the reduction of vasogenic oedema should always be considered for symptomatic control immediately. They may successfully reduce neurological symptoms before initiation of surgical or cytotoxic therapy and may also prevent symptoms during brain irradiation (18).

The role of chemotherapy in the treatment of brain metastases remains controversial.

An intact blood-brain barrier limits the penetration of standard chemotherapies into the central nervous system. However, the tight endothelial spaces of the blood-brain barrier are often disrupted by the presence of a metastasis. In the present case, brain metastases occurred under chemotherapy with PLD in the setting of systemic failure of chemotherapy. The limited therapeutic success in the treatment of brain metastasis with chemotherapy seems to be generally attributed to two factors: natural or acquired resistance to chemotherapy expressed by the tumor cells and delivery impediment related to the blood-brain barrier.

Chemotherapy resistance in ovarian cancer is not completely understood. Various studies have indicated that membrane transporter proteins, such as P-glycoprotein (MDR1), and DNA methylation and histone deacetylation are key factors in the development of chemotherapy resistance (7). Preclinical studies have demonstrated a significantly higher concentration of liposomal doxorubicin compared to conventional doxorubicin in normal and malignant brain tissue (8). Apart from the current observation, no other case report has commented on the occurrence of brain metastases during a systemic chemotherapy with PLD in a patient with recurrent EOC. Generally, most of the chemotherapeutics reach only a very low concentration in the cerebrospinal fluid (1, 2). Poor CNS penetration has been shown for anthracyclines such as idarubicin and daunorubicin (9) and platinum-analogues (10) in primates. However, in a study comparing F-DOX (free doxorubicin) and SL-DOX (stealth liposome–encapsulated doxorubicin), Siegal *et al*. found in a secondary brain tumor model a significantly higher (10-30 fold) concentration level after injection of SL-DOX than of F-DOX in the cerebospinal fluid of Fischer rats (11). It is unknown though if this concentration is sufficient for adequate tumor control. Nevertheless, laboratory and clinical studies have suggested that only a few cytotoxic agents with approved efficacy in ovarian cancer are able to cross the blood-brain barrier. Recent studies in patients with various solid tumours demonstrated a high concentration of topotecan, a topoisomerase I inhibitor, in the cerebrospinal fluid with measurable antitumour activity and objective response rates ranging from 33% - 63% (12, -019).

In conclusion, if patients with recurrent ovarian cancer suffer from new neurological symptoms the presence of brain metastasis must be excluded. EOC patients with brain metastases should receive multidisciplinary treatment. Randomized trials by international collaborative groups are warranted to define the real prevalence of brain metastasis and to define best therapeutic approach in this palliative setting.

References

1 Pectasides D, Pectasides M and Economopoulos T: Brain metastases from epithelial ovarian cancer: a review of the literature. Oncologist *11(3)*: 252-260, 2006.

2 Larson DM, Copeland LJ, Moser RP, Malone JM Jr, Gershenson DM and Wharton JT: Central nervous system metastases in epithelial ovarian carcinoma. Obstet Gynecol *68(6)*: 746-750, 1986.

3 Abrey LE and Dalmau JO: Neurologic complications of ovarian carcinoma: Cancer *85(1)*: 127-133, 1999.

4 Kumar L, Barge S, Mahapatra AK *et al*: Central nervous system metastases from primary epithelial ovarian cancer. Cancer Control *10(3)*: 244-253, 2003.

5 Biswas G, Bhagwat R, Khurana R, Menon H, Prasad N and Parikh PM: Brain metastasis-Evidence based management. J Cancer Res Ther *2(1)*: 5-13, 2006.

6 Cohen ZR, Suki D, Weinberg JS *et al*: Brain metastases in patients with ovarian carcinoma: prognostic factors and outcome. J Neurooncol *66(3)*: 313-325, 2004.

7 Balch C, Huang TH, Brown R and Nephew KP: The epigenetics of ovarian cancer drug resistance and resensitization. Am J Obstet Gynecol *191*: 1552-1572, 2004.

8 Rahman A, Husain SR, Siddiqui J *et al*: Liposome-mediated modulation of multidrug resistance in human HL-60 leukemia cells. J Natl Cancer Inst *84*: 1909-1915, 1992.

9 Berg SL, Reid J, Godwin K, Murry DJ, Poplack DG, Balis FM and Ames MM: Pharmacokinetics and cerebrospinal fluid penetration of daunorubicin, idarubicin, and their metabolites in the nonhuman primate model. J Pediatr Hematol Oncol *21(1)*: 26-30, 1999.

10 Jacobs SS, Fox E, Dennie C, Morgan LB, McCully CL and Balis FM: Plasma and cerebrospinal fluid pharmacokinetics of intravenous oxaliplatin, cisplatin, and carboplatin in nonhuman primates. Clin Cancer Res *11(4)*: 1669-1674, 2005.

11 Siegal T, Horowitz A and Gabizon A: Doxorubicin encapsulated in sterically stabilized liposomes for the treatment of a brain tumor model: biodistribution and therapeutic efficacy. J Neurosurg *83(6)*: 1029-1037, 1995.

12 Wong ET and Berkenblit A: The role of topotecan in the treatment of brain metastases. Oncologist *9(1)*: 68-79, 2004.

13 Pectasides D, Aravantinos G, Fountzilas G *et al*: Brain metastases from epithelial ovarian cancer. The Hellenic Cooperative Oncology Group (HeCOG) experience and review of the literature. Anticancer Res *25*: 3553-3558, 2005.

14 Kaminsky-Forrett MC, Weber B, Conroy T *et al*: Brain metastases from epithelial ovarian carcinoma. Int J Gynecol Cancer *10*: 366-371, 2000.

15 LeRoux PD, Berger MS, Elliott JP *et al*: Cerebral metastases from ovarian carcinoma. Cancer *67*: 2194-2199, 1991.

16 Deutsch M, Beck D, Manor D *et al*: Metastatic brain tumor following negative second-look operation for ovarian carcinoma. Gynecol Oncol *27*: 116-120, 1987.

17 Kim TJ, Song S, Kim CK, Kim WY, Choi CH, Lee JH, Lee JW, Bae DS and Kim BG: Prognostic factors associated with brain metastases from epithelial ovarian carcinoma. Int J Gynecol Cancer *17(6)*: 1252-1257, Epub 2007.

18 Lokich JJ: The management of cerebral metastasis. JAMA *234(7)*: 748-751, 1975.

19 Oberhoff C, Kieback DG, Wurstlein R, Deertz H, Sehouli J, van Soest C, Hilfrich J, Mesrogli M, von Minckwitz G, Staab HJ and Schindler AE: Topotecan Chemotherapy in Patients with Breast Cancer and Brain Metastases: Results of a Pilot Study. Onkologie *24(3)*: 256-260, 2001.

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