J Vet Clin 28(6) : 598-602 (2011)

Journal of Veterinary Clinics
www.ksvc.or.kr

Intraperitoneal Cisplatin Chemotherapy in A Canine Ovarian Cancer with Peritoneal Metastasis

Kyoung Won Seo, Jong Bok Lee, Su Ji Hong, Ye In Oh, Su Hyung Lee*, Hwa Young Youn and Goo Jang[1]

Seoul National University hospital for animals, the Research Institute of Veterinary Science
**Department of pathology, College of Veterinary Medicine, Seoul National University*

(Accepted: Dec 05, 2011)

Abstract : A 4-year-old female Shih-tzu dog weighing 5.1 kg was referred with abdominal distension and diagnosed as cystic papillary adenocarcinoma with metastasis to serosal surface of abdomen by biopsy. Intraperitoneal chemotherapy with cisplatin (50 mg/m^2) diluted in normal saline (250 ml/m^2) was initiated following removal of ascites one month after ovariohysterectomy (OHE). Clinical response was great and had no side effects during the chemotherapy period (3 relapses, 33 months after diagnosis). However, pleural effusion occurred with ascites and renal failure at the end of treatment. Eleven treatments of cisplatin were performed during 35 months after diagnosis. Intraperitoneal cisplatin instillation has been effective to control malignant ascites and pleural effusion in ovarian cancers and could be a reasonable palliative treatment. This is the first case report describing intraperitoneal cisplatin chemotherapy in metastatic ovarian cyst papillary adenocarcinoma in Korea.

Key words **:** chemotherapy, dog, malignant ascites, ovarian metastatic cancer.

Introduction

Ovarian neoplasms have relatively uncommon incidence in dogs because most dogs are neutered at an early age. Although the true incidence is unknown, the reported incidence rate is 6.25% in the intact female dog (5) and 0.5%-1.2% of all canine neoplasm (4,23).

They are recognized as three main categories depending on the histological criteria: epithelial-, germ- and sex cord stromal- cell. Epithelial cell tumors account for approximately 50% of ovarian tumors and have reported age range from 4 to 15 years (17,18,21). They include papillary adenomas, papillary adenocarcinomas, cystadenomas, cystadenocarcinomas, and undifferentiated carcinomas. These tumors are usually asymptomatic until the tumor volume is large enough to show mass effect and occasionally have ascites and pleural effusion depending on the metastasis to abdominal organ or thorax.

Ovariohysterectomy (OHE) is a treatment of choice and could be curative unless patients have signs of metastasis. If the tumor is benign, the prognosis may be good. However, in malignant case having transcoelomic spread of tumor, malignant ascites, pleural effusion, and other systemic signs due to metastasis to abdominal organ, the purpose of therapy would be palliative to reduce the clinical signs and increase the quality of life (QOL). A few palliative chemotherapies have been studied (9,10) although the efficacy of systemic chemotherapy and standard protocol has not been established for metastatic ovarian cancer in veterinary medicine.

Intraperitoneal chemotherapy with platinum chemotherapeutic drugs has been considered essential to manage cavitary human neoplasms with transcoelomic tumor spread or distant metastasis such as ovarian cancers (2,16). This cytotoxic treatment is based on the intraperitoneal administration of platinum drugs because cisplatin concentrations followed by intraperitoneal administration were higher than those by intravenous route in the omentum, small intestine, and diaphragm without increased toxicity (11).

This paper is to report a patient that was referred for malignant ascites from ovarian cystadenocarcinoma spread all over the abdomen and was successfully controlled by intraperitoneal palliative chemotherapy with cisplatin. The patient survived for 35 months after diagnosis.

Case

A 4-year-old female Shih-tzu dog weighing 5.1 kg was referred because of abdominal distension, no estrus cycles after first heat. On physical examination, it was noticed as clinically normal condition except enlarged abdomen. Abdominal ultrasonography revealed large amounts of ascites with moderately cellular contents and bilateral enlarged ovaries (Rt: 4.5 × 2.2 cm, Lt: 4.0 × 2.0 cm) with irregular margin and multifocal cysts. Hyperechoic materials with strong shadowing were also found in the corticomedullary junction and medulla of both kidneys. Abdominocentesis revealed an amber cloudy

[1]Corresponding author.
E-mail : snujang@snu.ac.kr

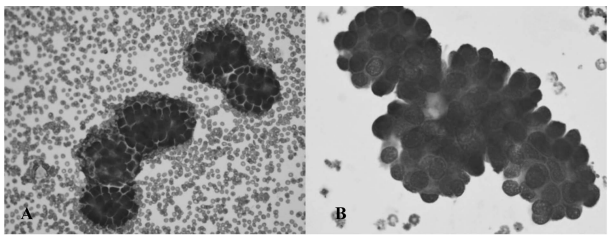

Fig 1. Cytology of the ovarian cancer. Ascites (A), Diff-Quik stain, × 400 and ovary (B), Diff-Quik stain, × 1000. Note clusters of epithelial cells collected by fine-needle aspiration with polyhedral- or flame-shape, variable amount of vacuolated cytoplasm, single round or oval nucleus with distinct one or two nucleoli. Chromatin pattern was coarse and frequent nuclear moldings were observed.

fluid that was determined to be an modified exudates (total nucleated cell count: 2,600/ul, total protein: 5.3 g/dl) containing predominant clusters of cells arranged in papillary, acinar, and tubular patterns and having uniform appearance as well as few neutrophils (Fig 1a). The enlarged ovaries also aspirated for cytology under ultrasound guidance and many large tightly cohesive clusters of cells having papillary-like structures, polyhedral- or flame-shape, variable amount of vacuolated cytoplasm, single round or oval nucleus with distinct one or two nucleoli, coarse patterned chromatin, frequent nuclear moldings were observed (Fig 1b). Complete blood count (CBC) with differential count, serum biochemical parameters were in reference ranges (Table 1).

Laparotomy was performed for OHE and exploration of abdominal organ. Numerous white firm nodules about 3-8 mm in size were seeded on the surfaces of the majority of abdominal parenchymal organs, peritoneum, and omentum. Both

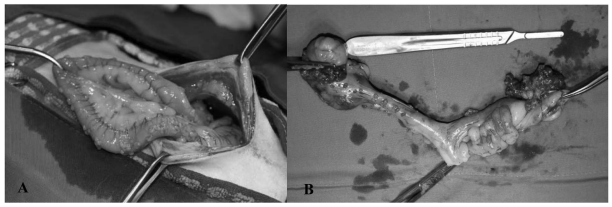

Fig 2. Gross appearance. (A) Numerous miliary nodules on intestinal serosa. (B) Gross appearance of affected ovaries and uterus. Symmetrically enlarged ovaries had pebble-like surface in the ovarian capsules with mixed brown color. The serosal surface of ovaries and uterus were covered with multiple nodules as well.

ovaries and uterus was carefully removed (Fig 2).The ovaries were enlarged symmetrically and had pebble-like surface in the ovarian capsules with mixed brown color. The serosal surface of ovaries and uterus were also covered with many multiple nodules. Portions of the ovarian mass and several peritoneal nodules were collected for histopathology. For histopathological examination, specimens were fixed in 10% buffered formalin, processed in a routine manner, embedded in paraffin, and stained with hematoxylin and eosin (H&E). Microscopically, the ovarian mass consisted of cystic structures lined by a single to multiple layers of cuboidal epithelial cells that made arboriform papillary projection into the cystic cavities (Fig 3). The neoplastic cells invaded connective tissue, stroma and cystic walls. The neoplastic cells had indistinct cell border and large amounts of eosinophilic cytoplasm. The nuclei of the neoplastic cells were round to oval and had one to two prominent nucleoli. Mitotic figure was rare and no tumor embolus was evident. Peritoneal nodules were composed of neoplastic cells having similar morphol-

Table 1. Changes of CBC and serum biochemical parameters on the patient

	Reference	2006-09-12	2008-02-11	2009-06-09	2009-08-11	2009-08-20
WBC	6000-17000/μl	8200	5990	11180	12310	12070
RBC	550-850 × 10^4/μl	588	585	539	593	502
Hb	10-18 g/dl	13.5	14.5	12.8	14.3	11.6
Hematocrit	35-55%	40	39.3	33.4	36	30.9
Platelet	12-60 × 10^4/μl	38.5	34.3	27.3	29.8	11.4
Na	142-154 mEq/L	151	148	147	141	134
K	4.0-5.4 mEq/L	4.2	4.4	3.9	5	5.6
Cl	105-119 mEq/L	112	115	113	105	100
ALT	10-100 IU/L	85			232	389
AST	0-50 IU/L	29			37	88
ALP	8-100 IU/L	99			580	631
BUN	7-27 mg/dl	15	17	33	40.4	54.6
Creatinine	0.5-1.8 mg/dl	0.8	0.9	1.5	1.7	2.6
Albumin	2.3-4.0 g/dl	3.2				2.5
T. protein	5.2-8.2 g/dl	5.7				4.4
Ca	7.9-12.0 mg/dl	8.8		11.4	10.7	10.3
IP	2.4-5.5 mg/dl	2.9		3.3	5.5	6.9

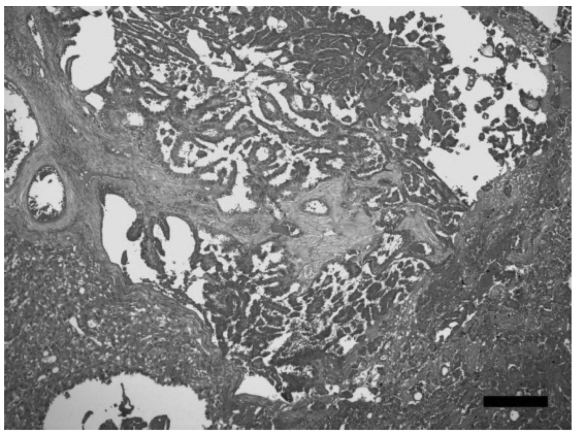

Fig 3. Cystic papillary adenocarcinoma of the ovary. The ovarian mass was composed with cystic structures lined by a single to multiple layers of cuboidal epithelial cells that made arboriform papillary projection into the cystic cavities. H&E, × 100, Bar = 2 mm.

ogy as that of the ovarian mass. Based on such findings, the ovarian mass was diagnosed as cystic papillary adenocarcinoma with abdominal seeding.

Intraperitoneal chemotherapy with cisplatin was initiated one month later after surgery. CBC, some serum biochemical parameters (blood urea nitrogen (BUN), creatinine), electrolytes, urinalysis were evaluated right before the chemotherapy. Dieresis with normal saline (18.3 ml/kg/h for 4 hours) prior to cisplatin instillation was performed. After removing of ascites that prevent diluted cisplatin from instilling as much as possible through 22 gauge over-the-needle catheter, the cisplatin (dosed at 50 mg/m^2 body surface area, total 17 mg) diluted in 250 ml/m^2 normal saline was given intraperitoneally through same catheter over 15 minutes at 10-20 ml/min under ultrasound guidance. After treatment, the dog was diuresed for an additional 4 hours with normal saline (3). Antiemetics (ondansetron 0.5 mg/kg IV, butorphanol 0.4 mg/kg IV) were given before cisplatin treatment. However, second chemotherapy was not performed by request of client until the abdominal distension was noticed again in 10 months after first chemotherapy. Clinical response was great and there were no signs of illness.

When abdominal distention recurred, abdominal fluid was aspirated and determined to be modified exudates (total nucleated cell count: 2,300/ul, total protein: 3.4 g/dl) containing large numbers of neoplastic epithelial cells. The dog was given cisplatin intraperitoneally with same method and 3 additional cisplatin treatments were performed at 4 week intervals. Complete response was achieved after 2nd chemotherapy by physical examination and abdominal ultrasonography. Clinical signs-free condition was lasted 9 months.

Malignant ascites recurred 9 months later and third chemotherapy with intraperitoneal cisplatin restarted 4 times every 4-5 weeks. The response to chemotherapy was good and achieved complete response again. However, at 2 months after 3rd cycle chemotherapy, malignant ascites was recurred with pleural effusion containing large numbers of neoplastic epithelial cells and cisplatin was delivered into abdomen and pleural effusion simultaneously. Clinical improvement was observed but did not achieve complete resolution of clinical signs during 4th cycle of intraperitoneal chemotherapy and body cavity fluid was slowly increased despite of cisplatin administration. After second administration of 4th cycle treatments, azotemia (BUN: 40.4 mg/dl, CRE: 1.7 mg/dl) was found and the aggressive fluid therapy was initiated. Although fluid therapy was effective to control azotemia, the volume of malignant ascites and pleural effusion was increased and removed by thoracocentesis and abdominocentesis as a supportive care. Eventually, azotemia was not controlled and the dog died 2 months after onset of azotemia and necropsy was not allowed. The survival time after diagnosis was 35 months.

During treatment period, intermittent anorexia was noticed after intraperitoneal administration and gastrointestinal signs such as vomiting and diarrhea were occasionally seen. However these symptoms were disappeared within 24 hours without treatment. Hematologic screenings were always checked before treatment and 7 days later from each treatment. WBC counts were below reference range after third therapy of second cycle (Table 1) but did not need preventative antibiotics and delay of the treatment. Acute renal failure was observed after total 11 intraperitoneal cisplatin treatments.

Discussion

Intraperitoneal chemotherapy with cisplatin was introduced to palliate metastatic cavitary neoplasia such as ovarian cancer in humans and many trials have showed higher cytotoxic levels in the peritoneal cavity than those in systemic circulation after instillation of drugs in a large volume through a semi-permanent catheter (20). Three large trials were performed in human with the ovarian cancer to compare intraperitoneal route with different agents to standard intravenous route. Although progression-free survival benefits were reported increased for IP administration, this chemotherapy has not been accepted as standard treatment due to unacceptable toxicity, neuropathy, and IP catheter failure (8,20). However, a few studies comparing IP versus IV route with other platinum drugs like carboplatin and additional paclitaxel are still ongoing because the previous studies had some problems on trial designs and toxicity evaluation (6,8).

Although successive palliative chemotherapy has been reported in an ovarian metastatic cancer and papillary cystadenocarcinoma (9), no effective and standard treatment methods have been recommended except OHE. Therefore, the prognosis of ovarian cancer with metastasis is considered poor and treatment focuses on improvement of QOL. This dog was initially intended for palliation of metastatic cancer in the abdomen by intraperitoneal chemotherapy, but response of cisplatin was excellent and clinical disease-free condition was lasted for 10 months at first instillation. Although limited reports were

described about intraperitoneal chemotherapy for metastatic ovarian cancer in dogs, palliative intracavitary cisplatin chemotherapies were described in dogs with ovarian carcinoma, papillary adenocarcinoma and pleural mesothelioma as to control of malignant ascites, tumor mass, survival times and toxicity (15,19). Because tissue concentration of cisplatin administered intraperitoneally in the outer 3 mm of tumor tissue exceeded those measured after higher dose intravenous administration and systemic therapy through intravenous route did not make high concentrations of cisplatin in the peritoneal cavity (7), intraperitoneal administration can be effective on the patient that have cancer spread in abdomen, especially epithelial ovarian cancer like human medicine.

Cisplatin is one of the platinum antineoplastic agents and has limited usage on systemic purpose attributed to severe toxicity such as nephrotoxicity, myelosuppression, vomiting and hypersensitivity. In this case, mild descent of WBC was observed during treatment. However, it recovered soon and never happened again. Gastrointestinal problems like vomiting, anorexia were sometimes found during treatment periods but those were very mild and manageable with antiemetic drugs. Although renal disease at the end of therapy was not confirmed by autopsy, it might be influenced by chronic accumulation of nephrotoxicity of cisplatin administration. However, it could occur spontaneously because treatment had been continued for almost 3 years and the nephrotoxicity was the rare problem caused by cisplatin administered intraperitoneally in human medicine (1,12,22). No information was provided as to the nephrotoxicity from intraperitoneal chemotherapy of cisplatin in veterinary medicine.

The delivered dose and volume of diluted cisplatin was 50 mg/m^2 and 250 ml/m^2, respectively and this method is originally for intrapleural cavity (3). In other veterinary reports, higher dose (70 mg/m^2) and larger diluted volume (1 L/m^2) were instilled and it may be advantageous to increase dose and volume for inducing maximum contact with cancer nodules in the peritoneal cavity (15,19).

Other platinum drug like carboplatin is a standard intravenous chemotherapeutic agent in human epithelial cancer and also studied for intraperitoneal administration. But previous reports showed that the response rate of cisplatin regimen was better than that of carboplatin and concluded that cisplatin may be superior to carboplatin when administered intraperitoneally (14). This result was attributed to the previous results that approximately 6-10 times more carboplatin was needed to reach equivalent tissue platinum concentration compared to cisplatin and carboplatin is usually used with lower dose compared to cisplatin (8,13). Therefore dose increasing could be necessary when using carboplatin intraperitoneally. Intraperitoneal carboplatin may be also applicable to veterinary medicine, dose adjustment with the same context and need to further investigation and trial.

In veterinary medicine, early neutering, frequent OHE for preventing genital disease and euthanasia make standardization of intraperitoneal chemotherapy difficult. However, to improve not only QOL but also survival time, intraperitoneal chemotherapy with cisplatin, carboplatin and other drugs like paclitaxel should be considered in canine patients that have metastatic ovarian cancer in abdominal or pleural cavity after optimal debulking of cancer.

Conclusion

A dog diagnosed as cystic papillary adenocarcinoma with metastasis to serosal surface of abdomen was treated with intraperitoneal chemotherapy with cisplatin following removal of ascites after OHE. Clinical response was great and survived for 35 months after diagnosis. Intraperitoneal cisplatin instillation could be a reasonable palliative treatment in metastatic ovarian cancer.

References

1. Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 2006; 354: 34-43.
2. Barber HR. New frontiers in ovarian cancer diagnosis and management. Yale J Biol Med. 1991; 64: 127-141.
3. Bonagura, J. Medical and surgical management of pleural effusion. In: Kirk's Current Veterinary Therapy: XIII Small Animal Practice. Philadelphia: WB Saunders. 2000: 819-825.
4. Cotchin E. Testicular neoplasms in dogs. J Comp Pathol 1960; 70: 232-248.
5. Dow C. Ovarian abnormalities in the bitch. J Comp Pathol 1960; 70: 59-69.
6. Echarri Gonzalez MJ, Green R, Muggia FM. Intraperitoneal drug delivery for ovarian cancer: why, how, who, what, and when? Oncology 2011; 25: 156-165, 70.
7. Esposito M, Campora E, Repetto M, Fulco RA, Simoni GA, Falcone A, et al. Regional pharmacokinetic selectivity of intraperitoneal cisplatin in ovarian cancer. Oncology 1988; 45: 69-73.
8. Fujiwara K, Markman M, Morgan M, Coleman RL. Intraperitoneal carboplatin-based chemotherapy for epithelial ovarian cancer. Gynecol Oncol 2005; 97: 10-15.
9. Greene JA, Richardson RC, Thornhill JA. Ovarian papillary cystadenocarcinoma in a bitch: case report and literature review. J Am Anim Hosp Assoc 1979; 15: 351-6.
10. Hayes A, Harvey HJ. Treatment of metastatic granulosa cell tumor in a dog. J Am Vet Med Assoc 1979; 174: 1304-6.
11. Lagrasse LD, Peretorius RG. The metabolism of cisdichlorodiammineplatinum, distribution, clearance, and toxicity. Am J Obstet Gynecol 1981; 139: 791-796.
12. Lesnock JL, Richard SD, Zorn KK, Krivak TC, Beriwal S, Sukumvanich P, et al. Completion of intraperitoneal chemotherapy in advanced ovarian cancer and catheter-related complications. Gynecol Oncol 2010; 116: 345-350.
13. Los G, Verdegaal EM, Mutsaers PH, McVie JG. Penetration of carboplatin and cisplatin into rat peritoneal tumor nodules after intraperitoneal chemotherapy. Cancer Chemother Pharmacol. 1991; 28: 159-165.
14. Markman M, Blessing JA, Major F, Manetta A. Salvage intraperitoneal therapy of ovarian cancer employing cisplatin and etoposide: a Gynecologic Oncology Group study. Gynecol

Oncol 1993; 50: 191-195.
15. Moore AS, Kirk C, Cardona A. Intracavitary cisplatin chemotherapy experience with six dogs. J Vet Intern Med 1991; 5: 227-231.
16. Neijt JP. Ovarian cancer treatment: time for some hard thinking. Eur J Cancer 1991; 27: 680-681.
17. Nielsen SW. Classification of tumors in dogs and cats. J Am Anim Hosp Assoc 1983; 19: 13-52.
18. Nielsen SW, Misdorp W, McEntee K. Tumours of the ovary. Bull World Health Organ 1976; 53: 203-215.
19. Olsen J, Komtebedde J, Lackner A, Madewell BR. Cytoreductive treatment of ovarian carcinoma in a dog. J Vet Intern Med 1994; 8: 133-135.
20. Ozols RF. Counterpoint: Intraperitoneal chemotherapy: an investigational treatment in ovarian cancer. J Natl Compr Canc Netw 2004; 2: 555-560.
21. Patnaik AK, Greenlee PG. Canine ovarian neoplasms: a clinicopathologic study of 71 cases, including histology of 12 granulosa cell tumors. Vet Pathol 1987; 24: 509-514.
22. Rothenberg ML, Liu PY, Braly PS, Wilczynski SP, Hannigan EV, Wadler S, et al. Combined intraperitoneal and intravenous chemotherapy for women with optimally debulked ovarian cancer: results from an intergroup phase II trial. J Clin Oncol 2003; 21: 1313-1319.
23. Sforna M, Brachelente C, Lepri E, Mechelli L. Canine ovarian tumours: a retrospective study of 49 cases. Vet Res Commun 2003; 27 Suppl 1: 359-361.

복강전이가 동반된 개 악성 난소암의 cisplatin 치료

서경원 · 이종복 · 홍수지 · 오예인 · 이수형 · 윤화영 · 장구[1]

서울대학교 수의과대학

요 약 : 네 살령의 암컷 시츄견이 복부 팽만으로 내원하여 조직검사 결과 cystic papillary adenocarcinoma로 진단되었으며, 복강 장간막으로의 전이도 확인되었다. 난소 자궁 적출술을 실시하고 1달 후, 복수를 제거한 후 cisplatin을 (50 mg/m^2)을 0.9% 생리식염수(250 ml/m^2)에 희석하여 복강내로 주입하였다. 치료기간 동안 3번의 재발이 있었으나, 임상증상의 개선이 매우 뚜렷하였으며, 특별한 부작용을 보이지 않고 진단 후 33개월 간 건강 상태를 유지할 수 있었다. 그러나 11번의 항암 치료 이후에 복수와 더불어 흉수가 병발하였고, 신부전증도 동반하였다. 수액요법과 대증치료의 일환으로 복강, 흉강 천자도 실시하였으나 개선을 보이지 않고 환자는 폐사하였다. 복강 내 cisplatin의 투여법은 난소 종양으로 인한 악성 복수, 흉수를 치료하는데 효과적인 완화요법으로 쓰일 수 있을 것으로 사료된다. 본 증례는 복강 전이를 동반한 악성 난소 종양이 발생한 환자를 복강 내 cisplatin투여를 통해 효과적으로 치료한 한국에서의 첫 번째 보고이다.

주요어 : 화학요법, 개, 악성 복수, 전이성 난소 종양