Metastatic and recurrent adenocarcinoma of the uterine cervix: a long-term survival of 16 years

I. Peregrin-Alvarez[1], *M.D.*; **M.N. Akl**[2], *M.D.*; **C.P. Morrow**[3], *M.D.*; **J.F. Magrina**[2], *M.D.*

[1]*Obstetrics and Gynaecology Department, De La Mujer Women's Hospital/Virgen Del Rocio University Hospital, Seville (Spain)*
[2]*Gynecologic Surgery Department, Mayo Clinic College of Medicine, Mayo Clinic, Phoenix, AZ*
[3]*Gynecologic Oncology Department, University of Southern California, Los Angeles, CA (USA)*

Summary

Purpose of investigation: Recurrent metastatic adenocarcinoma of the cervix is associated with an extremely poor prognosis. Treatment options for recurrent disease are limited and cure is extremely rare. *Case report:* We report a case of a 43-year-old patient with Stage IB adenocarcinoma of the cervix. She had multiple metastatic recurrence episodes salvaged with several radical surgeries, external and intraoperative irradiation, and chemotherapy over a survival period of 16 years. *Conclusion:* We conclude that long-term multi-modal salvage treatment may achieve longer survival in rare cases with recurrent metastatic adenocarcinoma of the cervix.

Key words: Metastatic adenocarcinoma; Recurrent adenocarcinoma; Long-term survival.

Introduction

Cervical cancer is the third leading cause of cancer-related death in women worldwide. The incidence of cervical adenocarcinoma has increased relatively compared to squamous cell carcinoma [1]. The prognostic significance of the adenocarcinoma cell type is still controversial. Chemotherapy remains the recommended treatment for recurrent or metastatic adenocarcinoma of the cervix that is not amendable to surgical resection or salvage radiation therapy. We present a case of cervical adenocarcinoma, with multiple recurrences salvaged with multiple multi-modal approaches over 16 years.

Case Report

A 43-year-old patient with Stage IB adenocarcinoma of the cervix underwent radical hysterectomy, bilateral salpingo-oophorectomy and bilateral pelvic lymphadenectomy in 1990. Pathology revealed moderately differentiated endocervical adenocarcinoma with microscopic parametrial invasion, and negative surgical margins and lymph nodes. She was randomized to the chemotherapy arm of a study comparing chemotherapy alone versus chemotherapy and pelvic irradiation. She received two cycles of bleomycin (32U daily day 1-4) and cisplatin (50 mg/m^2 day 4) followed by cisplatin (50 mg/m^2) every three weeks for two cycles. The patient remained disease-free for three years until 1993 when she was diagnosed with a small recurrence in the right upper vaginal wall without paravaginal extension. She was treated with surgical excision through a vaginal approach followed by external beam irradiation (4500 cGy) and vaginal brachytherapy (7352 cGy). Tumor margins were negative.

In 1995 she developed a recurrence in the same location but with paravaginal invasion. She underwent radical upper vaginectomy, partial resection of the bladder and right ureter with reimplantation. Tumor margins were negative for malignancy. She received postoperative brachytherapy to the pelvic sidewall (Iridium catheters, 3000 cGy) and pelvic external beam radiation (4000 cGy).

In 1997 she experienced a third vaginal recurrence in the same location. She underwent total infralevator pelvic exenteration with creation of a neovagina, ileal conduit, and sigmoid colostomy. Periaortic lymph nodes were excised and found to be negative. Tumor margins were negative for tumor. The patient remained disease-free for four years until 2001 when she had a recurrence in the anterior wall of the neovagina extending to the retropubic space, levator ani muscle and cecum. This was treated by radical resection of the neovagina, partial pubectomy and ileocecal resection. Margins were negative for tumor.

In 2002 she had an elevated CA-125 level (101 U/ml). PET scan revealed recurrence in the right inguinal lymph nodes. She underwent a right inguinofemoral lymphadenectomy. Pathology revealed nine out of 13 lymph nodes involved with adenocarcinoma. The patient received postoperative external beam radiation therapy (4860 cGy) to the right inguinal region. A few months later in 2002, she was diagnosed with metastasis to the left inguinal lymph nodes by PET scan. She underwent left inguinofemoral lymphadenectomy. Pathology revealed 13 out of 15 positive lymph nodes and she received postoperative external beam radiation therapy (5100 cGy) to the left groin.

In 2004 she was diagnosed with metastases in the mesentery of the sigmoid by PET scan after detection of an elevated CA-125 (192 U/ml). She received nine cycles of topotecan (0.75 mg/m^2 day 1-3) and cisplatin (50 mg/m^2) every three weeks. Subsequently, she had a normal CA-125 level (11 U/ml) and a negative PET scan.

In 2005 she developed recurrence in the aortic nodes and right ischial area diagnosed by PET scan. She received external beam radiation to the periaortic nodes and perineum (4000 cGy) with concurrent cisplatin (40 mg/m^2/week). Subsequently, a follow-up PET scan showed two suspicious areas around the ischial tuberosity. Both lesions were surgically excised. She received intraoperative radiation therapy (1250 cGy) and postoperative cisplatin (50 mg/m^2) for 3 cycles.

In 2006 the PET scan revealed multiple positive metastases in the retroperitoneal nodes, pubic bone, groin area and mediastinum. The patient received two courses of mitomycin (10

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Table 1. — *Combination chemotherapy for adenocarcinoma of the cervix.*

Author (year)	Chemotherapy regimen	Patients	RR	Complication (rate)	Mean survival-months (range)
Kavanagh (1987) [3]	Cisplatin: 50-60mg/m^2 5-FU: 500-800 mg/m^2 Doxorubicin:40-50mg/m^2	24	42%	G 3/4 neutropenia (38%)	6.1 (1-18)
Fanning (1995) [4]	Cisplatin: 90 mg/m^2 5-FU: 1500 mg/m^2 Ifosfamide: 3000 mg/m^2	9	78%	G 4 neutropenia (6%)	12 (3-36)
Zanetta (1997) [5]	Neoadjuvant chemotherapy Cisplatin: 50 mg/m^2 Epirubicin: 70 mg/m^2	20	55%	G 3/4 neutropenia (60%)	58% at 48 months
Umesaki (1999) [6]	Cisplatin: 50 mg/m^2 Mitomycin: 10 mg/m^2 Etoposide: 100mg/m^2 x 3	31	16%	G 3/4 neutropenia (45%)	10.8 (0.4-59.2)
Dimoploulos (2002) [7]	Cisplatin: 75 mg/m^2 + G-CSF Ifosfamide: 1500 mg/m^2 Paclitaxel: 175 mg/m^2	19	67%	G 3/4 neutropenia (26%) G 3/4 Anemia (13%) G 3/4 thrombocytopenia (7%) G 3/4 neurotoxicity (3%)	24.7
Fiorica (2002) [8]	Cisplatin: 20 mg/m^2 Topotecan: 0.75mg/m^2	11	27%	G 3/4 neutropenia (30%) G 3/4 thrombocytopenia (10%)	10 (1-41+)
Nagao (2004) [9]	Docetaxel: 60 mg/m^2 Carboplatin: AUC	6	86%	Grade 3/4 neutropenia (76%)	No Data available
Choi (2006) [10]	Cisplatin: 50 mg/m^2 Paclitaxel: 135 mg/m^2 Ifosfamide: 1500 mg/m^2	6	33%	G 3/4 neutropenia (13%) G 3/4 neurotoxicity (5%)	19 (11-26)

RR, response rate; 5-FU, 5-flurouracil; G, grade; G-CSF, granulocyte colony stimulating factor; AUC area under the curve.

mg/m^2, day 1) and irinotecan (100 mg/m^2/week), on a clinical trial, with improvement of metastatic lesions on a follow-up PET scan. A few months later in 2006, she died from a pulmonary embolus, 16 years after her initial diagnosis, but with extensive pulmonary metastatic disease.

Discussion

The management of recurrent and metastatic adenocarcinoma of the cervix remains a challenging problem. The relative infrequent occurrence of cervical adneocarcinoma has made the evaluation of different types of salvage therapy very difficult. Despite the multiple recurrences and surgical interventions, cycles of chemotherapy, overdosed pelvic irradiation, and aortic irradiation, we were able to achieve control of the recurrent sites over a long period of time.

Surgical excision in combination with pelvic irradiation appeared to be a viable option for the first recurrence due to being superficial and small in size. At the time of the second recurrence the patient declined pelvic exenteration, in spite of the increased risks for fistula formation with local radical excision after previous irradiation. She agreed to pelvic exenteration in 1997 after her third vaginal recurrence, and because there were no other viable alternatives. Additional surgical excisions in irradiated areas remained as the only option to maintain control of her disease. It is of interest, that in spite of multiple bilateral groin nodal metastases, she had no groin recurrences.

Chemotherapy is the mainstay treatment of recurrent and metastatic cervical adenocarcinoma not treatable by radiation or surgically not resectable. Previous studies on single agent chemotherapy for recurrent or metastatic cervical adenocarcinoma have shown response rates between 11% and 31% [2]. There are very limited data on combination chemotherapy for recurrent adenocarcinoma of the cervix. Recent studies have compared the response of squamous cell carcinoma and nonsquamous cell type to combination chemotherapy (Table 1). The authors noticed a lower response rate for the squamous cell carcinoma group compared to the nonsquamous cell type. The median survival of patients with squamous cancers was inferior compared with that of patients with other histologies [3-10].

Our patient was randomized to bleomycin and cisplatin after her initial surgery in 1990 and remained disease-free for three years. In 2004 she received nine cycles of topotecan and cisplatin and experienced clinical and radiographic evidence of disease remission. In 2005 she responded to concurrent chemoradiation with cisplatin, and in 2006 she had a partial response to mitomycin and irinotecan. CA-125 levels and fusion CAT\PET scan remained predictable and reliable in detecting recurrences and metastatic lesions during her disease.

Conclusion

Although recurrent and metastatic adenocarcinoma of the cervix is essentially an incurable disease, a multimodal salvage approach depending on the site of recurrence or metastasis may achieve long-term survival in rare cases.

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Address reprint requests to:
I. PEREGRIN-ALVAREZ, M.D.
Obstetrics and Gynaecology Department
Virgen Del Rocio University Hospital
Manuel Siurot Avenue
41013 Seville (Spain)
e-mail: iperegrina@sego.es