Single-agent Paclitaxel in Advanced Anal Cancer after Failure of Cisplatin and 5-Fluorouracil Chemotherapy

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Abstract. *Squamous cell cancer of the anal canal (anal cancer) is a rare disease but with worldwide increasing incidence. While combined therapy of 5-fluorouracil (5-FU), mitomycin, and radiation is the treatment of choice for locoregional anal cancer, the treatment of metastatic disease is less established. 5-FU and cisplatin combination has been adopted as the first-line treatment of choice for metastatic disease based on several phase II studies. However, no standard therapy has been established for stage IV anal cancer after the failure of this combination. Paclitaxel, a microtubule-stabilizing chemotherapeutic agent, has established clinical activity in squamous cell cancer of the head and neck. One prior report described the activity of paclitaxel in five patients with anal cancer. In this report, we describe our experience using this agent in seven patients suffering from metastatic anal cancer with prior progression on cisplatin and 5-FU. Four patients had an objective response and one patient experienced stable disease. Our results confirm activity of weekly-paclitaxel in patients with 5-FU and cisplatin-resistant metastatic anal cancer.*

The incidence of anal cancer is increasing worldwide and in the United States (1). An estimated 5,260 new cases (2,000 men and 3,260 women) were diagnosed and 720 patients succumbed to anal cancer in the United States in the year 2010 (2). The gold-standard therapy for locoregional anal cancer is 5-fluorouracil (5-FU), mitomycin C and radiation. This standard combination (Nigro protocol) has been established through the conduct of randomized phase III clinical trials (3-6). However, the treatment of patients with metastatic disease has been less established, partly due to the difficulty of conducting randomized studies in this limited patient population. Prospectively conducted phase II clinical trials have indicated significant clinical activity of 5-FU and cisplatin in the first-line treatment of metastatic anal cancer (7, 8). This combination has become the standard first-line treatment for metastatic anal cancer (9). There are no established chemotherapy treatments for patients with anal cancer after the failure of cisplatin and 5-FU. Paclitaxel, a potent microtubule-stabilizing agent, has known activity in a variety of squamous cell cancer types, such as cervical and head and neck cancers (10-17). One prior case series of 5 anal cancer patients reported clinical activity with this agent (18). We hereby report our own experience with paclitaxel monotherapy in the setting of cisplatin and 5-FU-resistant anal cancer (summarized in Table I).

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Case Reports

Case 1: A 47-year-old white male patient with history of receptive anal intercourse, alcohol abuse, chronic smoking, hepatitis C seropostivity, acquired immunodeficiency syndrome (AIDS) on highly active antiretroviral therapy (HAART) and with locally advanced anal cancer was treated with single agent 5-FU and radiation therapy with a complete response. Subsequently he developed bleeding per rectum and pain which was investigated with colonoscopy that revealed recurrent squamous cell carcinoma. This was salvaged with abdominoperineal resection. A second local relapse with multiple regional nodes involvement occurred one year later. The patient was treated with 5-FU and cisplatin with a good initial response but with eventual pelvic disease progression. He was then treated with paclitaxel at 80 mg/m^2/week for 3 weeks every 4 weeks without any substantial toxicity. The staging CT scan after the second cycle showed progressive disease. The patient opted for palliative care at that point and was referred to hospice care. The patient died 7 months from the initiation of paclitaxel treatment.

Case 2: A 54-year-old African American female who presented with pelvic pain was found to have a large anal

tumor with pelvic adenopathy and pelvic peritoneal implants. Her primary tumor was confirmed as squamous cell cancer. She was treated initially with chemoradiation (mitomycin C and 5-FU-based) in order to palliate her pelvic pain. The patient experienced an excellent radiographic response and was followed-up by observation. Six months later, she experienced clinical progression and was administered 5-FU and cisplatin. Disease control was achieved for a period of 4 months, followed by progression of her peritoneal disease. The patient was administered paclitaxel 80 mg/m^2/week for 3 every 4 weeks and achieved a partial response after 2 months of treatment (Figure 1). Her disease progressed after two more cycles of treatment and she was taken off treatment. The patient died 12 months after initiation of paclitaxel treatment.

Case 3: A 52-year-old Caucasian female patient with stage II anal cancer was treated with 5-FU and mitomycin C-based radiation with a complete response. Two years later, she developed back pain, and was diagnosed with vertebral metastases. A biopsy confirmed a poorly differentiated squamous cell cancer, consistent with her initial primary diagnosis. The patient was treated with palliative radiation, but unfortunately with further bony disease progression. She was subsequently treated with 5-FU and cisplatin with progressive disease. She was then treated with paclitaxel at 80 mg/m^2/week for 3 weeks every 4 weeks. Re-staging after two cycles confirmed stable disease, in association with reduction in bony pain. Progression occurred after four cycles (4 months) from paclitaxel initiation, with the development of new hepatic metastases. The patient was taken off treatment and enrolled in hospice care. She died 6 months after initiation of paclitaxel chemotherapy.

Case 4: A 49-year-old Asian male with history of AIDS, leuckoencephalopathy, perianal condyloma, and recurrent squamous cell carcinoma *in situ*, presented with pelvic pain. He was diagnosed with stage IV anal cancer with iliac bone and pulmonary metastases. He was treated with palliative radiation followed by 5-FU and cisplatin systemic chemotherapy. After 1 year of treatment, he developed progressive disease with progression of pulmonary metastases. He was treated with paclitaxel at 80 mg/m^2/week for 3 weeks every 4 weeks. He received six cycles with minimal toxicity and with a complete radiographic response. Treatment was discontinued after six cycles due to the development of grade 3 neuropathy. The patient experienced disease progression 2 months after treatment discontinuation and was referred to hospice care. He died 14 months after initiation of paclitaxel chemotherapy.

Case 5: A 57-year-old white male with a history of smoking, anal warts and receptive anal intercourse was diagnosed with metastatic anal cancer to the liver (biopsy-proven). He was treated with 5-FU and cisplatin for four cycles with good response but cisplatin had to be stopped due to toxicity. He was subsequently switched to 5-FU and mitomycin C with disease progression after two cycles. He was subsequently treated with paclitaxel at 80 mg/m2/week for 3 weeks every 4 weeks with a partial response lasting for 6 months. The patient is still alive at 16 months from the initiation of paclitaxel chemotherapy.

Case 6: A 60-year-old female diagnosed with stage III anal carcinoma was treated with mitomycin C and 5-FU-based chemoradiation. She had persistent local disease 3 months following completion of radiation, for which she underwent salvage abdomino-perineal resection. Three months after surgery, she had evidence of pelvic relapse for which she was treated with 5-FU and cisplatin. The patient had stable disease with eventual progression after 6 months of treatment. She was then treated with paclitaxel at 80 mg/m^2/week for 3 weeks every 4 weeks. Progressive disease was documented after two cycles of treatment. The patient died 5 months after the initiation of paclitaxel chemotherapy.

Case 7: A 43-year-old white female with prior hysterectomy for a benign ovarian tumor developed rectal bleeding. Work-up confirmed a T3N1 squamous cell cancer of the anal canal. She received chemoradiation as per the Nigro protocol with complete locoregional response. The disease progressed after 3 months with metastatic disease to the liver and she was started on 5-FU and cisplatin, with complete response after 8 months of treatment. She was subsequently followed up by observation, with progressive disease in the liver being documented 3 months from her last cisplatin-based therapy. The patient was treated on a clinical study with gemcitabine, calcitriol, and cisplatin for 6 months with eventual progression. She was then treated with paclitaxel at 100 mg/m^2/week for 3 weeks every 4 weeks. After two cycles of treatment, a re-staging CT scan showed a partial response. The patient continues on treatment with paclitaxel.

Discussion

This is the largest case series of paclitaxel monotherapy in patients with metastatic or recurrent anal cancer with progressive disease after 5-FU and cisplatin chemotherapy. Among seven patients treated with weekly paclitaxel chemotherapy, we have observed a radiographic objective response in four out of seven patients and one disease stabilization. Only two out of seven patients experienced progressive disease. Patients with a clinical radiographic benefit and baseline pain experienced considerable palliation. The duration of clinical benefit among patients with stable disease and partial response was variable and lasted between 4 and 6 months. Patients with partial or complete response appeared to

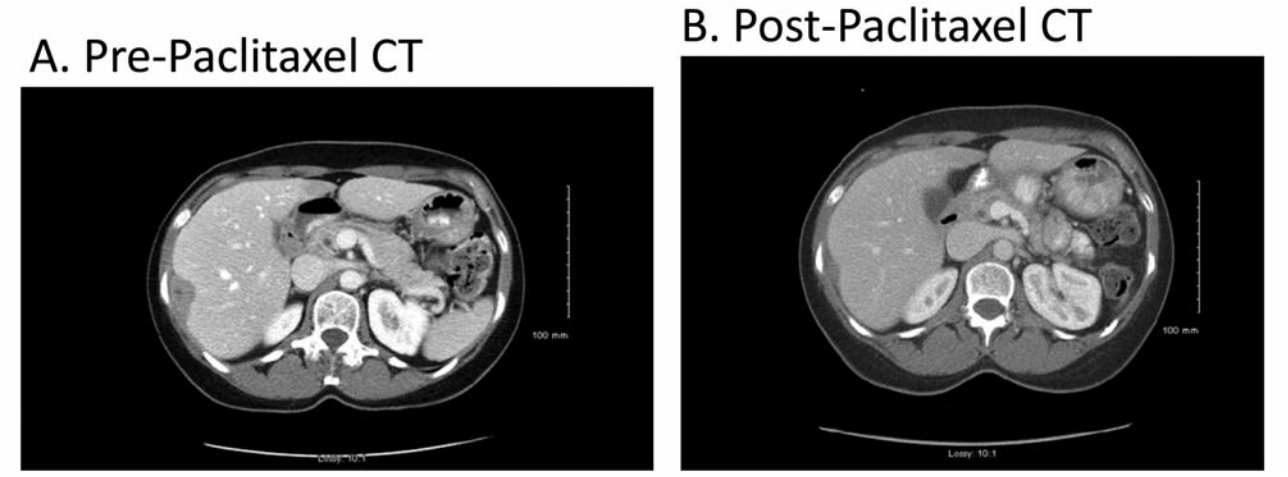

Figure 1. *Response in perihepatic tumor implant after two cycles of paclitaxel monotherapy. A: Pre-treatment. B: Post-treatment.*

Table I. *Paclitaxel outcome summary in 7 patients failing 5-FU and cisplatin.*

Case	Age (years)	HIV status	Response	PFS (months)	OS (months)
1	47	Positive	PD	2	7
2	54	Negative	PR	4	12
3	52	Negative	SD	4	6
4	49	Positive	CR	8	14
5	57	Negative	PR	6	N/A*
6	60	Negative	PD	2	5
7	43	Negative	PR	N/A	N/A**

PD: Progressive disease; PR: partial response; CR: complete response; SD: stable disease; PFS: progression free survival; OS: overall survival; N/A: not applicable as she is still under treatment. *alive, 14 months from initiation of paclitaxel; **Patient 7 is still on paclitaxel (4 months from initiation).

experience an improvement in overall survival (12-14 months). The observed efficacy in our series is consistent with the known activity of paclitaxel in other squamous cell cancer types such as head and neck and cervical cancers (10, 15, 19-23). One case series reported on the activity of paclitaxel in five patients with advanced anal cancer, two of whom were HIV positive (18). Three out of five patients achieved a partial response, with a clinical benefit ranging between 3 and 8 months. In contrast with our series, the regimen used in that series consisted of an every-3-week regimen of paclitaxel at 175 mg/m^2. The efficacy results were consistent with our series, suggesting clinical activity for paclitaxel in anal cancer on the weekly and every-3-week regimens. We conclude that paclitaxel monotherapy can be associated with a meaningful clinical benefit in patients with advanced anal squamous cell cancer who have progressed on prior 5-FU and cisplatin chemotherapy. The ease of administration and tolerance of weekly paclitaxel makes this regimen a reasonable option in the second-line treatment of advanced anal cancer. Prospective clinical trials would be needed to further define the clinical activity of this agent, whether as a monotherapy or in combination with other agents for anal cancer.

References

1 Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D: Global cancer statistics. CA: a cancer journal for clinicians *61*: 69-90, 2011.

2 Hurwitz H, Fehrenbacher L, Cartwright T, Hainsworth J, Heim W, Berlin J, Kabbinavar F, Novotny W and Scappaticci F: Wound healing/bleeding in metastatic colorectal cancer patients who undergo surgery during treatment with bevacizumab.

3 Bartelink H, Roelofsen F, Eschwege F, Rougier P, Bosset JF, Gonzalez DG, Peiffert D, van Glabbeke M and Pierart M: Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. J Clin Oncol *15*: 2040-2049, 1997.

4 Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on Cancer Research. Lancet *348*: 1049-1054, 1996.

5 James R, Wan S, Glynne-Jones R, Sebag-Montefiore D, Kadalayil L, Northover J, Cunningham D, Meadows H and Ledermann J: A randomized trial of chemoradiation using mitomycin or cisplatin, with or without maintenance cisplatin/5FU in squamous cell carcinoma of the anus (ACT II). J Clin Oncol (Meeting Abstracts) *27*: LBA4009, 2009.

6 Ajani JA, Winter KA, Gunderson LL, Pedersen J, Benson AB 3rd, Thomas CR Jr, Mayer RJ, Haddock MG, Rich TA and Willett C: Fluorouracil, mitomycin, and radiotherapy *vs*. fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. Jama *299*: 1914-1921, 2008.

7 Ajani JA, Carrasco CH, Jackson DE and Wallace S: Combination of cisplatin plus fluoropyrimidine chemotherapy effective against liver metastases from carcinoma of the anal canal. Am J Med *87*: 221-224, 1989.

8 Faivre C, Rougier P, Ducreux M, Mitry E, Lusinchi A, Lasser P, Elias D and Eschwege F: 5-fluorouracile and cisplatinum combination chemotherapy for metastatic squamous-cell anal cancer. Bull Cancer *86*: 861-865, 1999.

9 Engstrom PF, Arnoletti JP, Benson AB 3rd, Berlin JD, Berry JM, Chen YJ, Choti MA, Cooper HS, Dilawari RA, Early DS, Enzinger PC, Fakih MG, Fleshman J Jr, Fuchs C, Grem JL, Knol JA, Leong LA, Lin E, Mulcahy MF, Rohren E, Ryan DP, Saltz L, Shibata D, Skibber JM, Small W, Sofocleous C, Thomas J, Venook AP and Willett C: NCCN clinical practice guidelines in oncology. Anal carcinoma. J Natl Compr Canc Netw *8*: 106-120, 2010.

10 Kudelka AP, Winn R, Edwards CL, Downey G, Greenberg H, Dakhil SR, Freedman RS, Loyer E, Rusinkiewicz J, Gacrama P, Fueger R and Kavanagh JJ: Activity of paclitaxel in advanced or recurrent squamous cell cancer of the cervix. Clin Cancer Res *2*: 1285-1288, 1996.

11 Moore DH, Blessing JA, McQuellon RP, Thaler HT, Cella D, Benda J, Miller DS, Olt G, King S, Boggess JF and Rocereto TF: Phase III Study of Cisplatin With or Without Paclitaxel in Stage IVB, Recurrent, or Persistent Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study. J Clin Oncol *22*: 3113-3119, 2004.

12 Hitt R, López-Pousa A, Martínez-Trufero J, Escrig V, Carles J, Rizo A, Isla D, Vega ME, Martí JL, Lobo F, Pastor P, Valentí V, Belón J, Sánchez MA, Chaib C, Pallarés C, Antón A, Cervantes A, Paz-Ares L and Cortés-Funes H: Phase III Study Comparing Cisplatin Plus Fluorouracil to Paclitaxel, Cisplatin, and Fluorouracil Induction Chemotherapy Followed by Chemoradiotherapy in Locally Advanced Head and Neck Cancer. J Clin Oncol *23*: 8636-8645, 2005.

13 Forastiere AA, Leong T, Rowinsky E, Murphy BA, Vlock DR, DeConti RC and Adams GL: Phase III Comparison of High-Dose Paclitaxel + Cisplatin + Granulocyte Colony-Stimulating Factor Versus Low-Dose Paclitaxel + Cisplatin in Advanced Head and Neck Cancer: Eastern Cooperative Oncology Group Study E1393. J Clin Oncol *19*: 1088-1095, 2001.

14 Gibson MK, Li Y, Murphy B, Hussain MH, DeConti RC, Ensley J and Forastiere AA: Randomized Phase III Evaluation of Cisplatin Plus Fluorouracil Versus Cisplatin Plus Paclitaxel in Advanced Head and Neck Cancer (E1395): An Intergroup Trial of the Eastern Cooperative Oncology Group. J Clin Oncol *23*: 3562-3567, 2005.

15 Forastiere AA, Shank D, Neuberg D, Taylor SGt, DeConti RC and Adams G: Final report of a phase II evaluation of paclitaxel in patients with advanced squamous cell carcinoma of the head and neck: an Eastern Cooperative Oncology Group trial (PA390). Cancer *82*: 2270-2274, 1998.

16 McGuire W, Blessing J, Moore D, Lentz S and Photopulos G: Paclitaxel has moderate activity in squamous cervix cancer. A Gynecologic Oncology Group study. J Clin Oncol *14*: 792-795, 1996.

17 Rose PG, Blessing JA, Gershenson DM and McGehee R: Paclitaxel and Cisplatin as First-Line Therapy in Recurrent or Advanced Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study. J Clin Oncol *17*: 2676, 1999.

18 Alcindor T: Activity of paclitaxel in metastatic squamous anal carcinoma. Int J Colorectal Dis *23*: 717, 2008.

19 Hussain M, Gadgeel S, Kucuk O, Du W, Salwen W and Ensley J: Paclitaxel, cisplatin, and 5-fluorouracil for patients with advanced or recurrent squamous cell carcinoma of the head and neck. Cancer *86*: 2364-2369, 1999.

20 Moosmann P, Egli F, Stahel RA and Jost L: Weekly paclitaxel and carboplatin combination chemotherapy in patients with advanced squamous cell carcinoma of the head and neck. Onkologie *26*: 568-572, 2003.

21 McGuire WP, Blessing JA, Moore D, Lentz SS and Photopulos G: Paclitaxel has moderate activity in squamous cervix cancer. A Gynecologic Oncology Group study. J Clin Oncol *14*: 792-795, 1996.

22 Ferrari D, Fiore J, Codecà C, Di Maria G, Bozzoni S, Bordin V, Caldiera S, Luciani A, Zonato S, Floriani I and Foa P: A phase II study of carboplatin and paclitaxel for recurrent or metastatic head and neck cancer. Anticancer Drugs *20*: 185-190, 2009.

23 Basaran M, Bavbek SE, Güllü I, Demirelli F, Sakar B, Tenekeci N, Altun M, Yalçin S and Onat H: A phase II study of paclitaxel and cisplatin combination chemotherapy in recurrent or metastatic head and neck cancer. J Chemother *14*: 207-213, 2002.

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