Anal Fissures Associated With Targeted Therapies in Ovarian Cancer

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Although ovarian cancer remains a leading cause of gynecologic cancer death, targeted therapies are improving patient outcomes. Anal fissures are a side effect of targeted therapies that can disrupt or stop treatment regimens. Diagnosis and management of anal fissures by advanced practice nurses are crucial for maintaining the quality of life of patients with ovarian cancer.

Ovarian cancer is one of the most common gynecologic cancers after cervical cancer worldwide and is the leading cause of death from a gynecologic cancer in the western world. An estimated 21,000 new cases of ovarian cancer will be diagnosed and 15,000 people will die from the disease in 2009 (American Cancer Society, 2009). Most cases are diagnosed in women older than age 65. About 10% of ovarian cancers are hereditary and may be associated with a BRCA1 or BRCA2 mutation. Ovarian cancer has been thought of as the “silent killer,” but a consensus statement by the Gynecologic Cancer Foundation (2007) lists symptoms that may be present at diagnosis of early stage disease: bloating, pelvic or abdominal pain, difficulty eating, feeling full quickly, and urgent or frequent urinary symptoms. Women who have these symptoms for more than a few weeks should see their gynecologist.

Women who are diagnosed in the early stages of the disease have better outcomes. Favorable prognostic factors are younger age at diagnosis, good performance status, cell type other than mucinous or clear cell, stage I or II, well-differentiated tumor, smaller volume disease before or after debulking surgery, absence of ascites, and smaller residual tumor (less than 1 cm) following primary debulking surgery (Cain, El Masri, Gregory, & Kohn, in press; National Cancer Institute [NCI], 2009).

Treatment of ovarian cancer is directed by stage at diagnosis, grade of tumor, and treatment goals. Surgery is necessary for treatment as well as adequate staging and should be performed by a gynecologic oncologist. For stage IA or IB well-differentiated or moderately differentiated tumors, surgery alone may be adequate (Cain et al., in press). However, if the tumor is poorly differentiated or stage IC (positive ascites, surface involvement, physiologic or surgical rupture), adjuvant chemotherapy after debulking surgery is recommended; the systemic chemotherapy is based on platinums (cisplatin or carboplatin) in combination with a taxane, paclitaxel, or docetaxel (NCI, 2009).

For patients with stage III and IV disease at diagnosis, treatment may be directed by the outcome of surgery. Recommended treatment for a patient with optimally debulked (less than 1 cm residual disease at completion of surgery) is intraperitoneal (IP) chemotherapy with IP cisplatin, IP paclitaxel, and IV paclitaxel. The recommendation is based on the results from three randomized clinical trials (GOG-104, GOG-114, and GOG-172), which showed an increase in progression free survival and overall survival in patients receiving IP therapy (Alberts et al., 1996; Armstrong et al., 2006; Markman et al., 2001). GOG-172 demonstrated a median survival of 66 months on the IP arm versus 50 months on the IV arm. However, patients on the IP arm did experience increased toxicities of fatigue, pain, and hematologic, gastrointestinal, metabolic, or neurologic side effects as well as a significant decrease in their quality of life during treatment (Armstrong et al.).

For patients with suboptimally debulked stage III or IV disease, first-line treatment is platinum given in combination with paclitaxel (NCI, 2009). In recurrent or relapsed ovarian cancer, therapy choice depends on time to relapse or the platinum-free interval. If a patient recurs more than six months after the end of treatment with a platinum, she is considered platinum sensitive and retreatment with a platinum-containing regimen is recommended (NCI). If a patient recurs within six months of receiving a platinum, she is considered refractory to platinums and second-line therapies are considered. Second-line therapies include topotecan, liposomal doxorubicin, docetaxel, or gemcitabine. These drugs may be given alone or in combination. Consideration should always be given to available clinical trials (for more information, call +1-800-4-CANCER or visit www.clinicaltrials.gov).
Case Study

Ms. X, a 50-year-old Caucasian woman, presented to NCI with a history of incompletely staged, recurrent stage IA papillary serous ovarian cancer. Ms. X originally was diagnosed with papillary serous ovarian cancer in 2003 after emergent surgery for menorrhagia. A total abdominal hysterectomy and right salpingo-oophorectomy was performed for a cystic-appearing ovary. Pathology revealed a poorly differentiated serous papillary adenocarcinoma. The tumor was confined to the ovary without capsular interruption, and Ms. X was staged with IA grade 3. Complete surgical staging was not performed at that time.

Ms. X received adjuvant chemotherapy and completed six cycles of carboplatin and paclitaxel in July 2003. After completion of therapy, she underwent surgical assessment by a gynecologic oncologist in October 2003. The exploratory laparotomy included left salpingo-oophorectomy, appendectomy, pelvic and periaortic lymph node dissection, omentectomy, and washings. Pathology of the left ovary revealed a minute focus of subserosal tumor (less than 1 mm) and a few small neoplastic glands compatible with serous carcinoma. Evidence of persistent disease after neoadjuvant therapy suggested that Ms. X may have been at least stage IB at diagnosis, and perhaps more advanced.

Ms. X was without evidence of disease for one year until her CA-125 began to rise. A computed tomography (CT) scan revealed a 9 mm hypodensity in the left lobe of the liver and a questionable soft tissue density in the left anterior abdomen. She was considered to be platinum sensitive and was treated with six cycles of cisplatin and docetaxel. A CT scan at completion of treatment showed complete resolution of the surface implant in the liver and no evidence of abdominal or pelvic disease. One year later, Ms. X’s CA-125 was rising again; a CT scan showed a new peritoneal implant on the liver and increase in size of several lymph nodes, all less than 1 cm. Ms. X began anastrozole for four weeks. She underwent a secondary debulking with IP port placement and subsequently received four cycles of IP cisplatin. Ms. X was healthy for six months until her CA-125 began to rise again; she then was treated with three cycles of liposomal doxorubicin.

Unfortunately, Ms. X experienced severe palmar plantar erythema with desquamation of her trunk and axillae; as a result, she discontinued therapy.

Ms. X experienced altered bowel habits: constipation alternating with diarrhea. Her bowel movements were as infrequent as once every 24 hours to as often as five to six times per 24 hours. She had pain with defecation if she was constipated as well as mucus in the bowel movements. Ms. X denied any evidence of rectal bleeding or change in the color, consistency, or caliber of her stools. She did complain of intermittent vaginal spotting in the past six months, which required the use of a light panty shield. Otherwise, the review of systems was negative.

Medical history for Ms. X included gestational diabetes, endometriosis, depression, and gastroesophageal reflux disease. Past surgeries were cholecystectomy and tonsillectomy with adenoidectomy. Ms. X denied any family history of breast or ovarian cancers, but she had two grandfathers with throat and lung cancer. Her mother had valvular heart disease. Ms. X had undergone BRC4-mutation testing, which was negative. She worked full-time and had three children who lived at home.

She had a two-year history of smoking and two to four glasses of wine per month. Her allergies included a remote history of reaction to IV pyelogram dye, requiring premedication for CT scans. Ms. X’s current medications were escitalopram 10 mg by mouth daily, omeprazole 20 mg by mouth daily, and a multivitamin by mouth daily.

Ms. X’s general physical examination found her to be a healthy-looking woman in no apparent distress, with the exception of the following abnormal findings. Her abdomen was soft and nondistended and had a mid-line surgical scar from above the level of the umbilicus to the symphysis pubis. Bowel sounds were active and present in all four quadrants. Ms. X had hepatomegaly 1 cm below the costal margin. The abdomen was nontender, with no masses on palpation. A pelvic/rectal examination found external hemorrhoids and an 8 cm perirectal mass fixed to the right pelvic side wall. Complete blood count with differential, complete metabolic panel, amylase, lipase, and urinalysis all were within normal limits (CA-125 = 999 units/ml).

In February 2007, Ms. X enrolled in NCI trial 07-C-0058 (NCT00436215), a phase II study of sorafenib and bevacizumab in epithelial ovarian, fallopian, and peritoneal cancer. Sorafenib is an inhibitor of wild-type and mutant B-Raf and c-Raf kinase isoforms in vitro but also inhibits p58, c-kit, vascular endothelial growth factor receptor-2 (VEGFR-2) and platelet-derived growth factor receptor-β, affecting tumor growth as well as possibly promoting apoptosis (Singer et al., 2003). Bevacizumab is a humanized immunoglobulin G1 monoclonal antibody that binds all biologically active isoforms of human VEGF (VEGF or VEGF-A) with high affinity (Spannuth, Sood, & Coleman, 2008). In this trial, sorafenib was given orally 200 mg twice daily five days each week, and bevacizumab was given IV 5 mg/kg every two weeks on a 28-day cycle. Pyridoxine (vitamin B6) 100 mg orally twice daily was given at onset as prophylactic for the management of hand-foot syndrome (von Moos et al., 2008).

Prior to initiation of therapy at NCI, Ms. X’s evaluation included a CT scan, complete history and physical, and laboratory studies. Bimanual pelvic examination revealed a 10 cm perirectal pelvic mass. A CT scan of the chest, abdomen, and pelvis demonstrated multiple liver lesions, a 1.7 cm splenic lesion, and multiple peritoneal masses; the largest was a lobulated confluent mass (about 7 cm) in the pelvis adjacent to the rectum. Ms. X began therapy, and a CT scan of the chest, abdomen, and pelvis was repeated at the end of every two cycles. Physical examination, including a pelvic examination, was performed at every cycle.

After six weeks (1.5 cycles) of treatment, Ms. X reported increased rectal pain and several episodes of bright red blood on the toilet paper after bowel
movements. Findings on physical examination included an 8 cm pelvic mass and external hemorrhoids. Ms. X was referred for a flexible sigmoidoscopy, which revealed one external hemorrhoid, internal hemorrhoids, and compression of the rectum from known pelvic tumor. Stool softeners, docusate sodium 100 mg by mouth twice daily, were started. After two cycles of treatment, the study drug sorafenib was reduced to 200 mg once daily Monday through Friday because of recurrent hand-foot syndrome. Per protocol, vitamin B₆ was increased to 150 mg twice daily for management of hand-foot syndrome. After nine cycles of treatment, a CT of the chest, abdomen, and pelvis showed a partial tumor response; a partial response is at least a 30% reduction in the sum of the longest diameter of target lesions according to Response Evaluation Criteria in Solid Tumors version 1 criteria (Therrase et al., 2000).

Ms. X reported increased hemorrhoidal pain with intermittent bright red blood on toilet paper. Warm soaks and hydrocortisone 25 rectal suppositories were prescribed twice daily for one week, then at bedtime for one week. Rectal pain did not resolve with the use of suppositories or stool softeners. Surgery was consulted for an examination under anesthesia, revealing a severe, nonhealing anterior anal fissure with skin tags and no current external or internal hemorrhoids. The fissure ran the length of the anal canal with glistening, fibrous tissue at the base and no evidence of granulation or healing.

An anal block with bupivacaine hydrochloride and dilation to accommodate three fingers was performed. In addition to continuing docusate sodium and hydrocortisone rectal suppositories, vitamin B₆ was increased to 250 mg twice daily, and nitroglycerin 2% topical ointment was prescribed to increase blood flow to the area and promote wound healing, with directions to apply a pea-sized amount to the anterior portion of the anus daily. If headaches occurred, instructions were given to decrease the amount of nitroglycerin by 50%. At Ms. X’s first follow-up after the anal dilation, a repeat CT of the chest, abdomen, and pelvis confirmed a partial response in the size of her measurable lesions, including the pelvic mass. The intervention for the fissure decreased her pain with bowel movements; however, Ms. X discontinued the nitroglycerin ointment after just one week because of headaches.

After 16 cycles of treatment, a routine restaging CT scan demonstrated disease progression with interval development of new liver lesions and an increase in size of the pelvic mass adjacent to the rectum. The complication of anal fissure was ongoing, with symptoms worse because of increased diarrheal stools. Ms. X continued to manage her anal fissure pain conservatively with warm sitz baths, analgesics, and stool softeners.

**Anal Fissures**

An anal fissure is a longitudinal or elliptical split or tear in the long axis of the lower anal canal below the dentate line to the anal verge (see Figure 1). Fissures may be acute in nature (lasting less than six weeks) or chronic (present for more than six weeks) (Ayantunde & Debrah, 2006; Bhardwaj & Parker, 2007; Collins & Lunde, 2007). Features of a chronic anal fissure include sentinel skin tag or sentinel pile, hypertrophied anal papilla, an indurated edge, chronic granulation, exposure of the underlying internal anal sphincter, or anal scarring (Ayantunde & Debrah; McCallion & Gardiner, 2001). Fissures affect men and women equally; however, an anterior fissure is more likely to develop in women than men and is thought to be the result of obstetric injury (Ayantunde & Debrah). Most (87%) occur from ages 20–60. Ninety percent of fissures occur in the posterior midline where the skeletal fibers that circle the anus are weakest; 10% occur in the anterior midline (Collins & Lunde).

The pathophysiology of anal fissures is believed to be caused by increased toxicity of the internal anal sphincter or high resting pressure, which compresses the arteries that supply blood to the anoderm and results in local ischemia (McCallion & Gardiner, 2001; Utzig, Kroesen, & Buhr, 2003). Causes of anal fissure include passage of hard stool, chronic diarrhea, childbirth, habitual use of cathartics, anal trauma, radiation therapy, and surgery (Ayantunde & Debrah, 2006; Collins & Lunde, 2007). Frequency is higher in patients with syphilis, sexually transmitted diseases, tuberculosis, leukemia, Crohn disease, and HIV.

**Signs and Symptoms**

Patients with anal fissures often complain of pain described as a burning, cutting, or tearing after bowel movements. Bloody stools may or may not be present. If present, bright red blood appears on the surface of the stool or on toilet paper after wiping. Mucoid discharge and pruritis around the anus is common. Once the tear occurs, a cycle of repeated injury begins. The exposed internal anal sphincter muscle spasms, which causes pain and pulls apart the fissure, impairing healing. Consequently, patients may avoid defecation because of pain, which leads to passage of harder stool and the cycle repeats. Diagnosis of anal fissures is based on history and physical examination.

**Treatment**

Acute fissures often heal on their own within one to two weeks without intervention. Treatment of chronic fissures is more complicated in that the cycle of spasm and tearing of the mucosa must be broken for healing to occur. Medical treatment consists of three components: relaxation of the internal sphincter, institution and maintenance of painless stool passage, and pain relief. The WASH method (warm sitz baths after bowel movements, analgesics, stool softener, and high fiber diet) often is employed (Legall, 2007).

Topical nitroglycerin is used to help combat the issue of ischemia in anal
fissures by increasing local blood flow and decreasing sphincter pressure through vasodilatation. Several reviews have documented efficacy with its use (Ayantunde & Debrah, 2006; Bhardwaj & Parker, 2007; Collins & Lunde, 2007). No consensus exists on length of treatment necessary to heal anal fissures, ranging from four to 12 weeks (Brown, Taylor, Adam, & Shorthouse, 2002). Adherence is compromised because of side effects of headache, hypotension, and burning at application site (Ayantunde & Debrah; Utzig et al., 2003).

Injection of botulinum toxin has proven effective in treatment of chronic anal fissures. The toxin causes paralysis of muscles within hours and is injected into the internal or external anal sphincter to allow for relaxation by causing temporary synaptic blockade (Ayantunde & Debrah, 2006). The decrease in tone allows for healing of the fissure. Risks of botulinum injection include abscess at the injection site, temporary incontinence of urine, and flatus (Utzig et al., 2003). Calcium channel blockers, particularly nifedipine, have been used to influence smooth muscle contraction. Diltiazem hydrochloride in oral formulation as well as topical formulation (only available in Europe) also have been evaluated. Calcium channel blockers have comparable healing rates to topical nitroglycerin, but the oral formulation still has systemic side effects of headache and flushing, which lead to noncompliance (Utzig et al.). Anal dilation in the form of a four-finger stretch for four minutes has been used frequently; however, dilation is losing favor because of the high rate of sphincter damage and anal incontinence (Chong & Bartolo, 2008).

For patients with anal fissures that cannot be managed with conservative measures, surgery is an option. Fissurectomy can be performed with an open or subcutaneous technique, laterally or posterior. Fissurectomy and anal advancement flap are sphincter-conserving procedures that are more commonly used in anterior anal fissures. Healing rates of 90%-100% with low recurrence rates of 1%-3% have been reported in the literature (Chong & Bartolo, 2008).

Anal fissures are a unique skin toxicity encountered in phase I and phase II trials of bevacizumab in combination with sorafenib. Sorafenib and bevacizumab both target key signaling proteins involved in new blood vessel formation (angiogenesis). Angiogenesis is activated in cancer but also is a component of other pathologic processes (e.g., proliferative retinopathy, psoriasis) or normal processes (e.g., wound healing and development) (Annunziata, Azad, Hoskins, & Kohn, 2009). The persistence of the anal fissure in Ms. X may have been related to prior pelvic surgeries, altered anatomy from the extensive low pelvic mass, or reduced healing related to the combination therapy. Other common adverse events encountered in NCI’s phase I trial of bevacizumab in combination with sorafenib included hypertension, hand-foot syndrome, diarrhea, transaminitis, and fatigue (Azad et al., 2008).

To date, 57 patients have been treated in NCI’s phase I study and 25 patients have been treated in the phase II study of bevacizumab and sorafenib in epithelial ovarian, fallopian, and peritoneal cancers. Five of 57 patients in the phase I study experienced anal fissures at a range of two to nine cycles ($\bar{X} = 4.6$ cycles). Four of five patients had grade 1 anal fissure, and one patient had grade 2 anal fissure. Three of 25 patients in the phase II study experienced grade 1 anal fissures after two cycles. One additional patient reported anal fissure at baseline. The development of anal fissures was significant because bimanual pelvic examination became intolerable, pain precluded clinical analysis of disease, and the fissures were resistant to conservative or medical therapy.

**Conclusion**

Diagnosis and management of anal fissures by advanced practice nurses can directly influence the quality of life of patients on targeted therapies. All patients in the NCI clinical trials who developed anal fissures were managed conservatively and treated with stool softeners and rectal suppositories. One patient was treated by NCI’s surgical consult service with anal dilatation and topical nitroglycerin. None experienced complete resolution of the anal fissure while on treatment. Paramount to management of anal fissures is patient education regarding the chronic nature of the issue. Stressing conservative measures to promote nonpainful stool passage is key, with emphasis on the WASH method.

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**References**


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