Ultra short-term antimicrobial prophylaxis in patients undergoing surgery for gynecologic cancer

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Summary

Objective: To evaluate the efficacy of ultra short-term antimicrobial prophylaxis with ceftazidime in patients undergoing radical gynecologic surgery.

Patients and Methods: Two hundred patients undergoing surgery for a malignant disease of the female genital tract were enrolled in a prospective trial to receive 2.0 g ceftazidime as a single dose, 30 minutes before induction of anaesthesia. After surgery, each patient was assessed to confirm febrile status and the presence of infections at the surgical site, urinary tract and respiratory tract.

Results: Postoperative morbidity occurred in 23 patients (11,5%). Ten patients (5%) developed febrile morbidity, five (2,5%) vaginal cuff infections, four asymptomatic bacteriuria and two each wound infiltration and urinary tract infection. Twelve patients had microbiological evidence of infection and *Staphylococccus aureus* was the most common pathogen isolated. Univariate analysis demonstrated that pre-existing systemic disease, extensive blood loss (more than 500 ml) and long duration of surgery (more than 150 minutes) were the only factors associated with a significant increase in postoperative febrile morbidity.

Conclusions: Ultra short-term antimicrobial prophylaxis with ceftazidime is safe and effective in patients undergoing surgery for gynecologic cancer.

Key words: Radical gynecologic surgery; Antimicrobial prophylaxis; Ceftazidime.

Introduction

Infections are the most common morbid condition observed after gynecologic oncologic surgery and have been considered a major cause of death in patients with cancer [1]. The incidence of infectious morbidity, however, has dramatically decreased in the last decades due to the use of antibiotic prophylaxis which is commonly employed today [2].

Known risk factors for infectious morbidity in gynecologic cancer patients are age, concomitant systemic disease, previous chemotherapy or radiotherapy, pre-existing infections or alterations of cervico-vaginal flora, extensive surgery, blood loss greater than 1000 ml and use of drains and catheters [1, 3]. The most common pathogen agents in these infections come from the lower genital or intestinal tract and include anaerobs and gram-positive bacilli [4].

Numerous studies have been published in recent years about antimicrobial prophylaxis in gynecologic surgery, however the optimal drug and schedule for the different surgical procedures is still a matter of debate [3, 5-9].

The aim of this prospective study was to evaluate the efficacy of ultra short-term antimicrobial prophylaxis with ceftazidime in preventing infections following gynecologic oncology surgery.

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Patients and Methods

Eligible subjects for this prospective study were all patients scheduled to undergo surgery for a malignant tumor of the female genital tract between January 1999 and March 2001 at the Department of Obstetrics and Gynecology, University of Bari, Italy. Patients with suspected or known hypersensitivity to β-lactamine, those with elevated serum creatinine (> 2 mg/dl), sGOT (> 50 U/l) and sGPT (> 50 U/l) levels and patients who had received other parenteral antibiotics within seven days prior to surgery for a pre-existing infection (pelvic or systemic) were excluded from the study. The patients received verbal and written information concerning objectives of the trial prior to surgery and written permission was obtained. The study was approved by the ethical committee.

All subjects received a dose of intravenous ceftazidime (2.0 g), dissolved in 100 ml NaCl 0.9% and infused for ten minutes at the time of initiation of anaesthesia (20-30 min before incision). In case of extensive blood loss (> 1,500 ml) or when duration of surgery exceeded three hours, a second dose of the study medication was administered. All patients received mechanical bowel preparation and antithrombotic prophylaxis; povidone-iodine was used in the operating room to prepare the surgical field. Surgical precedures were always performed by two senior gynecologists.

Pre- and postoperatively haematological and biochemical examinations were performed, and each patient was assessed daily to confirm febrile status and the presence of infections at the surgical site, the urinary tract and the respiratory tract. The following criteria were applied to evaluate postoperative morbidity:

– *febrile morbidity* was defined as a rectal body temperature of ≥ 38°C recorded on at least two successive occasions (4-6 hours apart), excluding the first 48 hours after surgery;

– *infectious morbidity* was referred to as clinical evidence of one or more postoperative infections;

– *surgical wound infection* was described as the discharge of purulent material with or without culture of a pathogen according to the "ASEPSIS" scoring system [10].

– *urinary tract infection* was defined as a bacteriologically proven infection i.e. > 10^5 CFU/ml, with leukocytes in the sediment and one of the following signs of infection: fever > 38°C, urgency, frequency, dysuria or sopra-pubic tenderness;

– *asymptomatic bacteriuria* was defined as a bacteriologically proven bacteriuria (> 10^5 CFU/ml) without any signs of infection.

– *respiratory tract infections* were diagnosed by clinical signs and chest X-ray.

The following data were recorded on the patient's case record form: age, weight, concurrent or underlying disease, previous chemotherapy or radiation therapy, concomitant medication, surgical procedure, duration of surgery, estimated blood loss, drain positioning, vaginal packing, duration of catheterization and postsurgical medication. Antibiotic prophylaxis was considered successful if there were no signs or symptoms of infection postoperatively, and complications if any, recorded. All results were tabulated and statistical analysis was performed using the χ^2 test and Student's t-test as appropriate.

Univariate analysis was conducted in order to evaluate factors which could predicte post-operative infectious morbidity. Multivariate analysis was precluded by the small number of events.

Results

During the study period 257 patients were submitted to radical surgery for a malignant tumor of the genital tract at our Institution, but 57 were considered ineligible for one of the following reasons: 17 for known hypersensitivity to β-lactamine, 12 for elevated serum creatinine or GOT and GPT levels and 28 patients who had received other parenteral antibiotics within seven days prior to surgery.

The characteristics of the patients recruited for the study are shown in Table 1. Most patients were postmenopausal and had pre-existing systemic disease (i.e. diabetes, hypertension, tyreopathy or obstructive pulmonary disease). About 20% of the patients had received chemotherapy and or radiotherapy before surgery.

Table 1. — *Patient characteristics (mean ± sd).*

– Age (years)	58 ± 14
– Postmenopausal (%)	164 (82%)
– Weight (kg)	68 ± 15
– Associated systemic disease (patients)	62 (33%)
– Previous chemo-radiotherapy (patients)	40 (20%)
– Duration of operation (min)	160 ± 81
– Estimated blood loss (ml)	325 ± 26
– Days of catheterization	2.1 ± 1.9
– Use of drains (%)	80 (40 %)
– No. of days until discharge	7.3 ± 3.4

Primary tumors were almost equally distributed among ovarian, endometrial and cervical carcinomas. Seven percent of the patients had rare tumors: carcinomas of the fallopian tube, vagina and primary peritoneal (Table 2).

Table 2. — *Indications for surgery.*

– Cervical cancer	48 (24%)
– Endometrial cancer	62 (31%)
– Ovarian cancer	61 (30%)
– Vulvar cancer	15 (8%)
– Other	14 (7%)

Table 3 shows the surgical procedures employed in the study group. About half of the patients had total abdominal hysterectomy, with or without adnexectomy, omentectomy, peritoneal biopsies, pelvic and or para-aortic sampling or lymphadenectomy and abdominal debulking if indicated. Thirty-nine patients had some kind of radical hysterectomy (Class II-IV) according to the Rutledge classification.

Table 3. — *Surgical procedures.*

– Radical hysterectomies	39 (18%)
– Extrafascial hysterectomy ± debulking and omentectomy	102 (51%)
– Radical vulvectomy or wide local excision	15 (8%)
– Second-look laparotomy	24 (12%)
– Others*	20 (10%)

*Explorative laparotomy n = 6, second-look laparoscopy n = 5, small bowel resection n = 2, ureteroneocystostomy n = 3, inguino-femoral lymphadenectomy n = 4.

Due to long operative time (greater than 3 hours), 27 patients (13.5 %) received a second dose of the study medication. Overall 11 patients (5%) had discontinuation of the intestinal wall (n = 4) or urinary tract (n = 7), thus requiring further antimicrobial treatment following prophylaxis usually consisting of ceftazidime, 1 IV plus metronidazole, 250 mg IV three times a day for four days. Blood transfusions were necessary in 49 patients, 24.5% of the entire group. Three patients experienced serious postoperative complications requiring re-operation: one for hemoperitoneum and two for an intestinal fistula.

Febrile morbidity occurred in 23 patients as specified in Table 4: two patients (1%) developed wound infections; ten (5%) febrile episodes, two (1%) urinary tract infections, four (2%) asymptomatic bacteriuria and five (2.5%) vaginal cuff infections. There were no respiratory

Table 4. — *Infectious complications.*

– Febrile morbidity (%)	10 (5%)
– Wound infection (%)	2 (1%)
– Urinary tract infection	2 (1%)
– Asymptomatic bacteriuria	4 (2%)
– Vaginal cuff infection	5 (2,5%)
– Patients requiring antibiotic treatment	37 (18,5%)
– Patients re-hospitalized	4 (2%)

tract infections or septic deaths. Twelve patients had microbiological evidence of infection and *Staphylococcus aureus* was the most common pathogen isolated (50%). In the remaining six cases we found *Streptococcus pyogenes* in three patients, *Escherichia coli* in two and *Pseudomonas aeruginosa* in one patient with vaginal cuff infection.

Overall 37 patients (18.5%) of the study group received antibiotic treatment: 11 for discontinuation of the urinary or intestinal tract, three for postoperative complications and 23 for febrile morbidity.

Univariate analysis demonstrated that pre-existing systemic disease, extensive blood loss (more than 500 ml) and long duration of operation (more than 150 minutes) were the only factors associated with a significant increase of postoperative febrile morbidity (Table 5).

Table 5. — *Univariate analysis of factors that predict postoperative infectious morbidity.*

Factor	Patients with infectious morbidity (%)		P
– Age (years)	<58	13/100 (13%)	N.S.
	>58	10/100 (10%)	
– Postmenopausal	yes	17/164 (10%)	N.S.
	no	6/36 (17%)	
– Weight (kg)	<68	7/100 (7%)	N.S.
	>68	16/100 (16%)	
– Associated systemic disease	yes	20/62 (32%)	0.004
	no	3/138 (2%)	
– Previous chemo-radiotherapy	yes	7/40 (17%)	N.S.
	no	16/160 (10%)	
– Duration of operation (min)	< 150	4/106 (4%)	0.01
	> 150	19/94 (20%)	
– Estimated blood loss	< 500 ml	6/122 (5%)	0.04
	> 500 ml	17/88 (19%)	
– Days of catheterization	< 2	10/96 (10%)	N.S.
	> 2	13/104 (12%)	
– Use of drains	yes	10/80 (12%)	N.S.
	no	13/120 (11%)	
– No. of days until discharge	<7	10/98 (10%)	N.S.
	>7	13/102 (13%)	

N.S. = Not significant.

Discussion

Infections are the most common morbid condition observed after gynecologic oncologic surgery and have been considered a major cause of death in patients with cancer [1]. The most frequent septic complications of major gynecological surgery are febrile morbidity and pelvic cellulitis/endometritis [3-5]. Pathogenic microorganisms at the operative site are the most important determinants of the infections, since gynecological surgery is often performed through a glossly contaminated field [4]. The risk factors for infections following abdominal hysterectomy include prolonged procedures associated with technical difficulty and tissue trauma, sepsis existing at the time of the operation, and cancer that produces local immunosuppression thus making the use of prophylactic antibiotics neccessary [1].

Figures of infectious morbidity after debulking surgery in gynecologic cancer patients have rarely been reported in the literature. Heintz and colleagues reported fever or infection following surgery for ovarian cancer in 25% of the patients [9].

In a review of reported series, Hirsch found postoperative fever in 28%, 52% and 34% of patients submitted respectively to radical hysterectomy, radical vulvectomy and cytoreductive surgery for ovarian cancer [1]. In cervical cancer patients who had not received antibiotic prophylaxis the incidence of postoperative fever reached 52% of the patients. Marsden reported a surgical site-related infection rate of 3% after radical hysterectomy using a preoperative prophylaxis of 12 doses of cefoxitin given every eight hours [3]. Sevin and colleagues reported a rate of 15% of infections with the same regimen [7]. Patsner reported a 7% incidence of pelvic cellulitis with preoperative cefotetan [8]. Mayer *et al.* reported a 9% incidence of operative site infections among subjects undergoing radical surgery for gynecological cancers with one or three doses of piperacillin and tinidazole [5].

For this reason prophylactic administration of antibiotics in gynecologic surgery has been commonplace [2, 4], but the optimal schedule and drug is still a matter of debate.

Ceftazidime has a good in vitro activity against the microorganism involved in post-operative infectious complications, such as Gram negative bacilli and a certain activity against anaerobes [11, 12].

The choice of ultra short-term prophylaxis in our prospective study was based on two aspects: the lower cost compared to the short-term prophylaxis and the assumption that administration of the drug during induction of anaesthesia allows the best tissue distribution [1]. In a prospective randomized study, Lomeo and co-workers have demonstrated similar activity of ceftazidime used either as short-term prophylaxis (1 g three times perioperatively) or as ultra short-term (once before incision of the skin) in patients undergoing low-risk operations [12]. Colombo and colleagues reported that patients receiving two doses of antibiotics before radical surgery had a lower operative site infection rate and required antibiotic treatment less frequently [13]. An acceptable low rate of surgical site infections can be obtained with a two-dose antibiotic prophylaxis with a short half-life. Moreover, it has been reported that as few as three doses may significantly alter host flora and contribute to the development of selective resistance in the bacteria [4, 14, 15].

Antimicrobial prophylaxis with ceftazidime is feasible in patients undergoing surgery for gynecological cancers. In our study 57 patients were not eligible however previous infection and antibiotic treatment or elevation of

serum GOT, GPT and creatinine levels should not be considered a contraindication to the use of cephalosporins.

In our experience the incidence of postoperative morbid events (UTI, febrile episodes, wound infections and asymptomatic bacteriuria) was quite low (11%), and similar to that reported by other authors [1-9], suggesting that the regimen is effective.

Overall 37 patients (18.5%) of the study group received antibiotic treatment. Among these patients it was not possible to reduce the number of those who required antibiotic treatment for infections of the urinary or intestinal tract and for postoperative complications. However precise knowledge of the risk factors for development of febrile morbidity in the remaining 23 patients may further reduce this number. As univariate analysis demonstrated that pre-existing systemic disease, extensive blood loss and long duration of the operation are the only factors associated with a significant increase in postoperative febrile morbidity, these conditions should be taken in to account for further antibiotic treatment before febrile morbidity occurs.

The results of our study suggest that ultra short-term antimicrobial prophylaxis with ceftazidime is feasible and effective in patients undergoing surgery for a malignant disease of the female genital tract. Further studies are necessary to confirm our preliminary results, to evaluate new schedules of treatment and to select those patients who require further antibiotic treatment following prophylaxis.

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