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ORIGINAL ARTICLE

Urinary Tract Infections in Patients with Solid Tumors: Retrospective Study

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Abstract

Purpose: Urinary tract infection (UTI) is one of the most common infections in patients with cancer. It may occur at different phases of the disease and results from the interaction of several factors. The objective of our study was to determinate the particularities of these infection in this special population.

Patients and Methods: Retrospective study including all patients followed for solid tumor in the medical oncology department CHU Habib Bourguiba Sfax who had developed at least one episode of UTI documented between 2017 and 2019.

Results: Forty-six patients were collected: 24 women and 22 men. The median age was 57 years. A history of diabetes and urolithiasis were found in 23.9% and 19.6% of cases respectively. The site of the primary tumor waspelvic in 30 cases (65.3%), including 17 bladder tumors, and extra-pelvic in the other cases. Ten patients (21.7%) had recurrent episodes of UI during their follow-up, including 8 cases of bladder tumors. Urinary catheters was used in ten cases. All the patients had received at least one line of chemotherapy. The majority of UTIs (82.6%) occurred during cycles of chemotherapy, 26% of which were associated with febrile neutropenia. The most common bacteria was *Escherichia coli* (58.6%) which was resistant to cefotaxime and ciprofloxacin in 25% and 39.3% of cases respectively. Seven patients (15%) presented polymicrobial UTIs. The urine contained at least one multi-resistant germs in 26.1% of cases more frequently in pelvic tumors then extra-pelvic tumors (36.2% versus 6.2%; p = 0.035), in the presence of urinary catheter (70% versus 13.9% in the absence of catheter; p = 0.001) and during chemotherapy (35.7% versus 6.2% apart from chemotherapy; p = 0.02), the UTI was complicated of bacteremia in 6 cases (13%), four of which were undergoing chemotherapy and three were associated with febrile neutropenia, resulting in one case in septic shock and death.

Conclusion: It seems necessary, following this study, to implement recommendations for treatment and prevention of UTIs in solid tumors. They must be particularly adapted to the level of risk incurred by the different risk factors.

Keywords

Cancer, Infection, Urinary tract

Introduction

Urinary tract infections (UTIs) are one of the most frequent infections in patients with solid tumors. Although prolonged and profond neutropenia due to chemotherapy is rare, several factors increase the risk of infection in patients followed for solid tumors and the association of multiple risk factors is not uncommon [1]. In addition, specific factors was described in this particular population such as urinary stasis secondary to obstruction caused by tumor progression, disruption of natural anatomical barriers and immunosuppression secondary to anti-cancer treatments. The increasing use of medical devices may promote these infections [2]. The epidemiology of these infections changes over time with the emergence of multi-resistant germs and polymicrobial infections are more frequently isolated. Given their frequency and their severity in a particularly fragile population, new therapeutic or even preventive approaches must be developed [3,4]. The objective of our study was to study the epidemiological and microbiological particularities of UTIs in patients with solid tumors.

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Table 1: Distribution according to the site of the primary tumor.

Site of the Primary Tumor	Number	Tumor's Type (Number)
Pelvic	30	Bladder tumor (17) Ovarian tumor (5) Cervical tumor (3) Low rectal tumor (2) Prostate tumor (1)
Extra-pelvic	16	Digestive tract tumors other than rectum (8) Metastatic Breast tumor (3) Metastatic Lung tumor (2 others (5)

Patients and Methods

The study was a retrospective analysis of the data of all the patients followed in the medical oncology department of the Habib Bourguiba Sfax University Hospital, Tunisia for a solid tumor who had developed at least one episode of UTI documented and confirmed by a Cytobacteriological examination of Urine between January 2017 and December 2019. The definition criteria for an UTI are the presence of clinical signsand a bacteriuria greater or equal to 10^5 germs per ml or with a lower bacteriuria (10^3 to 10^4 germs per ml), but associated with a leukocyturia of at least 10^4 per ml.

For each UTI episode, we collect:

- Patient clinical data:
  - History: Such as urogenital anomaly, diabetes, bladder outflow obstruction, urodynamic anomalies…
  - The site of the solid tumor: Pelvic (bladder tumor, genital, anorectal) or extra-pelvic tumor, stage of disease at the time of the onset of the UTI episode
  - The presence or not of a medical device such as vesical catheter, ureteral stents or nephrostomy tube
  - The number of UTI episodes, time of onset (during or apart from systemic treatment) and revelating clinical signs
- Microbiological data:
  - The germs identified in each episode of UTI
  - A multi-microbial UTI was to be mentioned
  - Data of the antibiograms which were carried out for each isolated germ which were classified to sensitive or resistant character to the studied antibiotics

Data analysis was performed using 20th version of SPSS. The qualitative variables were expressed as percentages and the quantitative variables as the mean ± standard deviation after checking the normality of the distribution, and as the median if not (the non-Gaussian distribution). The Fisher or chi 2 test were performed for the comparison of qualitative variables. A p-value less than 0.05 was defined as the level of statistical significance.

Results

Forty six 46 cases were collected. The median age was 57 years, most (73%) aged more than more than 50 years. A female predominance (52%) was noted. A history of diabetes and urolithiasis was found in 23.9% and 19.6% of cases respectively. The site of the primary tumor was pelvic in 30 cases (65.3%), including 17 cases of bladder tumors, and extra-pelvic in the other cases (Table 1). All pelvic tumors other than bladder tumors were locally advanced. The majority of UTIs occurred at an advanced stage of the disease with 69.6% of the tumors were metastatic. Irritative urinary signs such as dysuria were the main revelating symptoms in 80.4% of cases. A systematic bacteriological investigation in the presence of an isolated fever was the reason for the discovery in 7 cases.

A medical device was present in ten cases (21.7%). It was a percutaneous nephrostomy tube in all cases used for decompression of ureteral obstruction due to their tumors.

Ten patients (21.7%), presented recurrent UTIs during their follow-up, including 8 cases (80%) of bladder tumors and 4 cases (40%) with nephrostomy tubes. The number of episodes varied from 2 to 5. A total of 60 UTIs were then diagnosed.

Different bacterias were isolated from urine (Table 2). The most frequent was *Escherichia coli* (58.6%) followed by *Klebsiella pneumoniae* (28.2%), *Enterococcus faecalis* (23.9%) and *Pseudomonas aeruginosa* (17.3%). Strains of *Escherichia coli* were resistant to ampicillin, cefotaxime, and ciprofloxacin in 67.8%, 25% and 39.3% of cases, respectively. Strains of *Klebsiella pneumoniae* were resistant to cefotaxime and imipenem in 18.75% and 15.38% of cases, respectively. Strains of *Pseudomonas aeruginosa* were resistant to ceftazidime, imipenem and ciprofloxacine in 12.5% for each antibiotic. All strains of *Enterococcus faecalis* were

Table 2: Spectrum of bacterias isolated from urine.

Bacteria	Number (%)
Escherichia coli	27 (58.6)
Klebsiella pneumoniae	13 (28.2)
Enterococcus faecalis	12 (26)
Pseudomonas aeruginosa	8 (17.3)
Enterococcus faecium	4 (8.6)
Enterobacter cloacae	3 (6.5)
Streptococcus agalactiae	2 (4.3)
Staphylococcus aureus	2 (4.3)
Proteus mirabilis	1 (2.1)
Acinetobacter baumannii	1 (2.1)
Salmonella spp	1 (2.1)

sensitive to ampicillin and glycopeptides (Table 3). The antibiotic treatment is initially prescribed on a broad spectrum based on cefotaxime with aminoglycoside then it would be adapted according to the antibiogram result.

All the patients received at least one line of chemotherapy. The majority of UTIs (32 cases, 82.6%) occurred during the cycles of chemotherapy, of which 12 cases or 26% were associated with grade 3 or 4 febrile neutropenia from the World Health Organization (WHO). These episodes of febrile neutropenia were all treated in hospital with broad-spectrum intravenous antibiotics. A protocol based on Gemcitabine and platinum used in the treatment of bladder tumors, whether metastatic or not, was the most implicated

Table 3: Susceptibility to antibiotics of the most frequent bacterias isolated.

Antibiotic	*Escherichia coli*		*Klebsiella pneumoniae*		*Enterococcus faecalis*		*Pseudomonas aeruginosa*	
	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant
Ampicillin	32.2%	67.8%	-	100%	100%	-	-	-
Amoxicillin and clavulanic acid	58.33%	41.67%	60%	40%	-	-	-	-
Ticarcillin	32.79%	67.21%	-	100%	-	-	100%	
Ticarcillin and clavulanic acid	61.67%	38.33%	62.5%	37.5%	-	-	87.5%	12.5%
Piperacillin	32.76 %	67.24%	-	100%	-	-	85.71%	14.29%
Piperacillin and Tazobactam	82.26%	17.74%	68.75%	31.25%	-	-	100%	-
Mecillinam	84.75%	15.25%	92.86%	7.14%	-	-	-	-
Cefalexin	61.67%	38.33%	81.25%	18.75%	-	-	-	-
Cefoxitin	94.59%	5.41%	80%	20%	-	-	-	-
Cefuroxime	75.41%	24.59%	81.25%	18.75%	-	-	-	-
Cefixime	76.27%	23.73%	81.25%	18.75%	-	-	-	-
Cefotaxime	75%	25%	81.25%	18.75%	-	-	-	-
Ceftazidime	75.41%	24.59%	81.25%	18.75%	-	-	87.5%	12.5%
Cefepime	80%	20%	81.25%	18.75%	-	-	87.5%	12.5%
Aztreonam	80.36%	19.64%	81.25%	18.75%	-	-	100%	-
Ertapenem	100%	-	87.5%	12.5%	-	-	-	-
Imipenem	100%	-	84.62%	15.38%	-	-	87.5%	12.5%
Meropenem	100%	-	87.5%	12.5%	-	-	-	-
Gentamicin	85.45%	14.55%	66.67%	33.33%	-	-	100%	-
Tobramycin	79.31%	20.69%	71.43%	28.57%	-	-	100%	-
Amikacin	95%	5%	92.86%	7.14%	-	-	100%	-
Netilmicin	87.1%	12.9%	68.75%	31.25%	-	-	-	-
Tigecycline	100%	-	-	-	-	-	-	-
Nalidixic Acid	51.67%	48.33%	62.50%	37.5%	-	-	-	-
Norfloxacin	63.64%	36.36%	71.43%	28.57%	-	-	-	-
Ciprofloxacin	60.66%	39.34%	66.67%	33.33%	-	-	87.5%	12.5%
Trimethoprim	55.74%	44.26%	53.8%	46.2%	-	-	-	-
Trimethoprim-Sulfamethoxazole	57.14%	42.86%	53.8%	46.2%	-	-	-	-
Fosfomycin	97.83%	2.17%	100%	-	-	-	-	-
Furans	100%	-	71.43%	28.57%	-	-	-	-
Colistin	-	-	10%	90%	-	-	-	-
Glycopeptide	-	-	-	-	100%	-	-	-

in 12 cases (31.5%) not associated in all cases with neutropenia. It was a palliative chemotherapy in 28 cases (73.6%).

Seven patients (15.2%) presented polymicrobial UTIs. All of them had pelvic tumors and 4 cases had percutaneous nephrostomy. Mycosic infection by candida was associated in 2 cases (one patient with diabetes and metastatic bladder tumor, apart from any chemotherapy and a second patient with no particular history, with a metastatic prostate tumor having developed 5 episodes of UTI during his follow-up, which developed during chemotherapy in a context of febrile neutropenia a three-germ UTI associating *Klebsiella pneumoniae*, *Enterococcus faecalis* and *Candida albicans*).

We identified at least one multi-resistant germ in 26.1% of cases. A significant difference in this rate of strain resistance was noted between pelvic tumors and extra-pelvic tumors (36.2% versus 6.2%; p = 0.035), a single episode of UTI or recurrent episodes of UTI during follow-up (8.4% vs. 70%; p <0.0001), with or without urine medical devices (70% vs. 13.9%; p = 0.001) and underway or apart from chemotherapy (35.7% vs. 6.2%; p = 0.02). There was no significant difference between males and females (p = 0.48) or in patients < or > 50 years (p = 0.62).

Six UTI episodes were complicated with bacteremia, four of which were undergoing chemotherapy, four with nephrostomy tube and three cases of febrile neutropenia. One case was complicated with septic shock and death. The germs isolated in these 6 cases were equally distributed between *Escherichia coli*, *Klebsiella pneumoniae* and polymicrobial UTI. Half of them were multi-resistant strains.

Discussion

This study allowed to observe the epidemiology and microbiology of UTIs in a specific population which are patients with solid tumors. Although solid tumors are much more common, infections in this population are not as well studied as in malignant hemopathy and they constitute a much more heterogeneous population which makes these studies difficult [5,6]. Specific factors have been described and the presence of multiple risk factors in the same patient is not uncommon [1,7,8].

The risk factor most described in the literature for both solid tumors and hematologic malignancies is neutropenia [1,9]. It is defined as a neutrophil count below 2000 cells/mm^3. The risk of developing infections is significant in the presence of WHO grade 3 neutropenia and major in grade 4 neutropenia which are defined by a number less than 1000 and 500 cells/mm^3 respectively. The most common cause of neutropenia is chemotherapy. It can also occur after radiation therapy or the administration of other myelosuppressants (eg, ganciclovir). Neutropenia is the most serious haematological toxicity of anti-cancer treatments, often limiting the doses to be better tolerated. The degree and duration of neutropenia determine the risk of infections [10]. According to studies published in the literature, patients with solid tumors that develop febrile neutropenia are considered in the majority of cases to be at low risk of infection [11,12]. In our study, 82.6% of UTI episodes occurred during cycles of chemotherapy, WHO grade 3 or 4 febrile neutropenia was associated in only 26% of cases.

Specific guidelines for the management of febrile neutropenic patients with underlying solid tumors have recently been published [13]. They stress the importance of performing risk assessment in order to identify low-risk patients who can be treated in an ambulatory setting, since hospitalisation is associated with exposure to nosocomial infections, often with multi-resistant germs. However, the safety of this ambulatory treatment should only be implemented if an appropriate infrastructure is present [14,15]. On the other hand, the identification of high-risk patients allows them to be managed by appropriate antibiotic therapy under adequate monitoring. The risk still being the evolution on septic shock, which can be fatal [16]. Three UTI episodes (6%) in our neutropenic patients were complicated with bacteremia, leading in one case to a septic shock and death.

Another risk factor associated with an increase UTIs incidence described in solid cancers is the destruction of normal anatomic barriers. Indeed, the human body has normal anatomical barriers such as the skin and various mucous surfaces (oropharyngeal, gastrointestinal, respiratory and genitourinary) which provide an important natural defense mechanism against pathogens [17]. The innate responses use phagocytic cells (neutrophils, monocytes, and macrophages), cells that release inflammatory mediators (basophils, mastcells, and eosinophils), and natural killer cells. The molecular components of innate responses include complement, acute-phase proteins, and cytokines such as the interferons. Anti-tumor treatment such as chemotherapy often damages the mucous membranes thereby increasing the risk of infections caused by microorganisms that colonize their surfaces (e.g., viridans group streptococci (VGS), *Streptococcus pneumoniae*, *Stomatococcus mucilaginosus*, enteric Gram-negative bacilli (GNB), and anaerobes] [1]. In our study, the majority of UTIs occurred during chemotherapy treatment. The most frequent germs were enteric GNBs (*Escherichia coli* (58.6%), *Klebsiella pneumoniae* (28.2%) and *Enterococcus faecalis* (26%)).

These barriers can also be damaged by radiation therapy, surgery and the use of medical devices frequently used in cases of urinary obstruction or incontinence. These devices frequently promote acute or even chronic UTIs, sometimes progressing to

bacteremia [18-20]. Eradication of these UTIs is often difficult and recurrence is the rule [21]. Ten cases (21.7%) in our studyhad percutaneous nephrostomy to treat an obstructive renal failure secondary to their tumors, thus promoting these UTIs. Recurrent episodes were objectified in 4 of them (40%). A complication with bacteremia was noted in 40% of cases. Prophylactic antibiotic therapy may then be necessary in these cases, especially in recurrent episodes [1]. Regardless of all of these factors, the tumor itself may be the direct cause of these anatomical barriers breaking down. It can cause local erosions and form fistulas, for example vesico-vaginal or vesico-rectal fistulas, which can be the case with locally advanced pelvic tumors.

In addition, obstruction caused by tumor extension is an independent factor favoring different types of infections [1]. The site most frequently affected by these obstructions is the urinary tract [22]. The resulting urine stasis leads to bacterial colonization and can progress to UTIs. Acute or chronic ureteral obstruction (most often unilateral but sometimes bilateral) is often the result of a retro-peritoneal or pelvic tumor developing. Quick removal of this obstruction is required. In our study, the site of the primary tumor was mostly pelvic in 30 cases (65.3%), with 17 bladder tumors. Whatever the anticancer treatment was for a curative or palliative purpose, the treatment of the urinary tract infection is an emergency in front of the risk of sepsis with a treatment of the cause to avoid recurrences and contribute to therapeutic efficacy.

Polymicrobial UTIs have been described in the literature. They most often occur in the elderly, immunosuppressed, people with long-term medical devices, HIV infection, people with tumors and diabetes [22]. Seven of our patients (15.2%) presented polymicrobial UTIs. They were pelvic tumors in all cases, 4 of them with percutaneous nephrostomy tubes. Mycotic UTIs have also been described [23,24]. They generally occur in association with a bacterial UTI with similar risk factors which are immunosuppressive treatments, diabetes, the presence of a foreign medical device but also the use of antibiotics, in particular broad-spectrum antibiotics [25]. A candida was isolated in 2 cases (one patient with diabetes and metastatic bladder tumor, apart from any chemotherapy and a second patient with no particular history, with a metastatic prostate tumor having developed 5 episodes of UTI during his follow-up, which developed during chemotherapy in a context of febrile neutropenia a three-germ UTI associating *Klebsiella pneumoniae*, *Enterococcus faecalis* and *Candida albicans*). Treatment of these infections is always difficult.

Another major problem which concerns these UTIs in patients with solid tumors but also in the general population is the resistance to antibiotics. A review of the literature by Tenney J, et al. published in 2018 described the most common risk factors for this resistance [26]. The most described risk factor was the previous use of antibiotics but also the long-term use of medical devices, a previous hospitalization, an age over 50 years, recurrent UTI, both male and female sexes, immunosuppression and uncontrolled diabetes. These risk factors are frequently observed in patients with solid tumors. In our study, we identified multi-resistant strains in 26.1% of cases. A significant difference in this rate was noted between a single episode of UTI or recurrent episodes of UTI during follow-up (8.4% versus 70%; $p < 0.0001$), in the presence or not of medical devices (70% versus 13.9%; $p = 0.001$) and during or apart from chemotherapy (35.7% versus 6.2%; $p = 0.02$) and there is no significant difference between men and women ($p = 0.48$) according to data from the literature. An additional risk factor was identified which is the tumor site (36.2% for pelvic tumors versus 6.2% for extra-pelvic tumors; $p = 0.035$) which can be referred to the recurrent nature of UTIs in pelvic tumors. Otherwise, we did not note any significant difference according to age < or > of 50 years ($p = 0.62$).

Conclusion

The management of UTIs in patients with solid tumors is complex. The risk factors favoring these infections are multiple and often associated. The presence or not of deficiencies in the host's immune system as well as the nature of the germ(s) identified and their sensitivity to antibiotics determine the types of complications likely to develop. It therefore seems necessary, according to this study, to implement recommendations for the treatment and prevention of UTIs in cancer. They must be particularly adapted to the level of risk incurred by these various risk factors. It is very important to know the cause of UTI as well as the gateway to treat it effectively. Urinary tract obstruction is the most common cause.

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