INCIDENCE OF URINARY INFECTIONS IN PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES UNDERGOING ANTINEOPLASTIC THERAPY

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SUMMARY:
Some of the most common complications encountered in patients with haematological malignancies are infectious diseases which are the leading cause of death for more than 75% of these patients. Among these, urinary tract infections (UTIs) are some of the complications that are common in these patients. These may be caused by chemotherapy and neutropenia induced by bone marrow invasion by malignant cells or they may be the result of existing co-morbidities. This retrospective study relies on data processed from a total of 1194 patients with haematological malignancies, hospitalized in the Clinic of Haematology, City Hospital Timisoara between January 2002 - March 2009. Incidence of urinary tract infection in these patients (21.1%) shows a significantly increasing trend compared to the general population (1-3%), with higher incidence rates in women. Both genders also showed high rates of incidence of other conditions that increase susceptibility to such infections. The germ most frequently involved was E. coli (81%). Urinary tract infections in these patients caused high occurrence of episodes of acute renal failure or aggravation of chronic renal failure. In conclusion, the incidence of UTI is high in patients with haematological malignancies undergoing chemotherapy and their evolution is relatively severe due to the existing immunosuppression that can significantly affect kidney function.

Key Words: urinary tract infections; antineoplastic therapy; haematological malignancies

Rezumat:
Unele dintre cele mai frecvente complicații întâlnite la pacienții cu boli hematologice maligne sunt reprezentate de complicațiile infecțioase, acestea constituind principala cauză de deces pentru mai mult de 75% dintre acești bolnavi. Dintre acestea, infecțiile tractului urinar reprezintă unele dintre complicațiile întâlnite la acești pacienți. Acestea se pot datora atât neutropeniei induse de către curele de tratament cu citostatice aplicate și de invadarea măduvei osoase cu celule maligne, cât și afecțiunilor concomitente bolii de bază. Pentru realizarea acestui studiu retrospectiv au fost prelucrate datele unui număr de 1194 de pacienți cu hemopatii maligne internați în perioada ianuarie 2002- martie 2009 în Clinica de Hematologie a Spitalului Municipal Timișoara. Incidența infecțiilor tractului urinar la acești pacienți (21.1%) este semnificativ crescută raportată la populația generală (1-3%) și prezintă o afectare mai mare a sexului feminin. În cazul ambelor sexe a fost semnalată, în proporție ridicată, prezența și a altor afecțiuni cu rol de factor favorizant al infecției urinare. Germenul cel mai frecvent implicat a fost E. Coli (81%). Infecțiile tractului urinar la acești pacienți a determinat apariția unor episode de insuficiență renală acută sau acutizări ale insuficienței renale cronice într-un procent crescut. În concluzie, incidența ITU este crescută la pacienții cu boli hematologice maligne aflați sub chimioterapie, evoluția acestora fiind relativ severă datorită imunosupresiei existente, putând afecta semnificativ funcția renală.

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INTRODUCTION

Haematological malignancies cause a number of heterogeneous pathological conditions resulting from the proliferation of cancer cells in the bone marrow and lymphatic system. Worldwide, approximately 250,000 people are diagnosed annually with leukaemia which represents 2.5% of total cancer cases (1). Of these, chronic lymphocytic leukaemia (CLL) is the most common form encountered in adults and represents about 30 - 40% of all forms of leukaemia. The incidence of the illness in Western countries is about 2-4 cases per 100,000 inhabitants, with 30% higher occurrence in men than women. Chronic myeloid leukaemia has an incidence of 1-2 cases per 100,000 persons per year and is more common in men, mainly targeting middle-aged and elderly patients. The incidence of malignant Hodgkin lymphoma is 3 to 100,000 inhabitants in the U.S. and Western European countries (1). The incidence of malignant non-Hodgkin’s lymphoma in the world has increased by about 80% since the early 70s, which makes it the third cause of cancer in children, the fifth in women, and the sixth in men (1). Multiple myeloma has an incidence of about 5.72 cases per 100,000 inhabitants in EU countries and it represents 1% of total neoplasia and 10% of all haematological malignancies (1). The incidence of haematological malignancies in Romania is approximately 3-4 cases per 100,000 inhabitants.

Some of the most frequent complications encountered in patients with haematological malignancies are infectious diseases, which - especially in case of acute leukaemia - are the leading cause of death in more than 75% of these patients (2, 3). Immune deficiencies seen in these patients, associated with the immuno-suppressive effects of chemotherapy, generate a major risk for infections (11). Several conditions that increase the susceptibility of these patients to infections have been described. These include: neutropenia induced by bone marrow invasion by malignant cells but also due to chemotherapy, with the risk of infection being directly linked to the severity and duration (2-7). In most patients, the induction diet with chemotherapeutics will determine the occurrence of neutropenia within the following 2-3 weeks, when approximately 60 - 80% of the patients are at risk of developing infectious episodes, with the percentage dropping to half during the remission-consolidation therapy. (2, 3). It is estimated that 80% of confirmed infections in patients with neutropenia are caused by endogenous flora (2,3). T-cell deficiencies, such as those encountered in malignant non-Hodgkin’s lymphomas or induced by long-term corticosteroid therapy represent an additional risk factor for infectious diseases (2-7). Splenectomy determines a decrease in antibody response. Chemotherapy-induced mucositis, the use of vascular catheters, administration of blood and derivatives are among other factors that increase susceptibility to infections in these patients. Several studies show an association between recurrent infections and hypogammaglobulinemia particularly common in CLL, multiple myeloma and myelodysplastic syndromes (6, 8-10).

Humoral immune dysfunctions give a predisposition to infections with encapsulated germs (Hemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitides). Cell immunity deficiencies favour a wide range of bacterial infections (Mycobacterium spp, Nocardia spp, Listeria monocytogenes, Salmonella spp), fungal infections (Pneumocystis jiroveci, Cryptococcus neoformans, etc.), protozoan infections (Toxoplasma gondii), viral infections (cytomegalovirus, Epstein-Barr and chicken pox-zoster virus). Qualitative or quantitative phagocyte defects (including neutropenia) frequently co-exist with Gram-positive bacterial infections (Staphylococcus aureus, Streptococcus spp), Gram-negative bacterial infections (Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter spp) or fungal infections (Candida spp, Aspergillus spp.) (2, 3, 7)

Besides respiratory, digestive, systemic and dermatological infections, urinary tract infections (UTIs) are frequent complications encountered in patients diagnosed with haematological malignancies and under cytostatic therapy. Although frequently seen in practice, in general, UTIs in patients with haematological malignancies are merely mentioned alongside other infections. They are very scarcely treated as such in the literature. Since we had a significant number of cases available for research, we wanted to look at UTIs in these patients within a specific period of time. It is a known fact that these are inflammatory diseases caused by the penetration and abnormal proliferation of pathogens in the urinary tract, manifested by bacteriuria.

In multiple myeloma, due to humoral immune dysfunction, the risk of bacterial infections is high, with the most frequent occurrences being respiratory infections with Gram-positive bacteria (Streptococcus pneumoniae pneumonia) and Gram-negative UTIs, especially after initiation of chemotherapy (19).

The agents most commonly involved in the aetiology of urinary infections in patients with haematological malignancies are Gram-negative germs. Most urinary infections are caused by Escherichia coli -
Enterobactericeae family, which is part of the normal intestinal flora and accounts for approximately 75 - 80% of urinary infection cases in patients without catheters, urologic abnormalities or calculi. Pseudomonas aeruginosa has a particular place especially after 1980 (12). Other Gram-negative bacteria belonging to the same family are involved in a smaller percentage in the aetiology of uncomplicated urinary infections: Proteus, Klebsiella and Enterobacter (occasionally). These are involved especially in recurrent infections and infections associated with urological maneuvers, stones or obstruction.

Gram-positive germs (Staphylococcus aureus, Staphylococcus epidermidis) and streptococcus play a less substantial role in urinary tract infections. There are also rare cases of urinary infections caused by Gram-positive germs: Corynebacterium jeikeium, Bacillus, Leuconostoc, Lactobacillus, Propionibacterium acnes and Rhodococcus species (13).

Fungal pathogens (Candida, Aspergillus, Fusarium), too, are frequent in neutropenia patients. The risk of fungal infections is correlated with the duration and severity of the neutropenia, the number of cytostatic diets and the duration of antibiotherapy (14).

A number of known urinary infection-favouring factors may be present as well:

- local: renal stasis, urinary tract obstructions (congenital malformations, tumors), polycystic kidney disease, kidney stones, urine discharge disturbances (bladder-urethral reflux), bladder function disruption, catheterization and instrumental exploration of the urinary tract;
- extra-urinary: immunosuppression (immune deficiency), protein and vitamin deficiencies, sexual intercourse and pregnancy, poor perineal hygiene, genital and prostate conditions, neurological conditions, chronic digestive and gallbladder conditions, metabolic (diabetes mellitus, gout, nephrocalcinosis, oxaluria, hypovitaminosis A), essential hypertension, etc (20-23).

The objective of this research is to evaluate UTIs in patients with known haematological malignancies undergoing cytostatic therapy, with various treatment schemes.

**MATERIALS AND METHODS**

A total of 1194 patients hospitalized in the Hematology Clinic of Timisoara Municipal Hospital between January 2002-March 2009 were analysed in a retrospective study. In terms of diagnosed haematological disease, a number of 331 cases of non-Hodgkin’s lymphoma, 179 cases of Hodgkin’s lymphoma, 232 cases of chronic lymphocytic leukemia, 74 cases of chronic myeloid leukaemia, 19 cases of acute lymphatic leukaemia, 50 cases of acute myeloid leukaemia, 97 patients had multiple myeloma, 15 cases have been diagnosed with Waldenstrom macroglobulinemia, 16 cases of myeloid metaplasia myelofibrosis, 66 with polycythemia vera, 61 cases of essential thrombocytosis were analyzed. Considering that myelodysplastic syndromes are a heterogeneous group of diseases that belong to a pre-leukaemia condition at high risk of developing into acute myeloblastic leukaemia (17,18), 54 cases of refractory anemia with blast excess under chemotherapy were included. (We should mention that these cases showed blasts and were under chemotherapy, therefore they were included in the study under haematological malignancies).

During the respective period, these patients were dynamically monitored with each of them having at least four hospitalizations.

When evaluating the presence of an UTI, we mainly looked for presence of urine cultures with bacteriuria >= 100 000/ml (significant bacteriuria by Kass), alongside the presence of the clinical and biological picture, including leukocyturia in the urine. The clinical-biological picture of UTI was difficult to assess, as it would frequently overlap the picture of the disease: fever is commonly seen in haematological malignancies, and so is the inflammatory syndrome. We should mention that the infectious clinical picture and leukocyturia were not relevant in all patients. For this reason, the quantitative urine culture was the defining element in our study for diagnosing UTI in the patients included in the study.

With a view to analysing inducing or favouring factors, paraclinical tests conducted were monitored as well – such as blood tests (urea, creatinine, blood count, ESR, uric acid) and abdominal ultrasound used in diagnosing renal lithiasis. Another element we looked at was the presence of other conditions that could have been the causes of changes in the body’s defence mechanisms (senescence, presence of chronic liver or kidney disease, diabetes, splenectomy, another associated neoplasia, cytostatic therapy, corticosteroids, neutropenia).

Statistical analysis was performed using SPSS 10 and Open Epi 2.3 programs. Unpaired student t test was used for the comparison of the mean values and Chi Square test for percent values. Values of p<0.05 were considered significant.
RESULTS

The 1194 patients with haematological malignancies analyzed within January 2002 and March 2009 had the following distribution per age and gender: 571 of the patients (47.8%) were female, aged 16 to 88 (with their age average being 55.16±16.35 y) and 623 were male (52.2%), aged 16 to 91 (with their age average being 56.33±15.8 y).

Urinary infection was identified in 253 subjects, amounting to 21.1% of the studied patients. Out of these, 145 were women (57.3%) and 108 men (42.8%). An additional number of 244 cases showed insignificant bacteriuria, with the urinary germs count being less than 10^5 colony-forming units CFU/ml(Fig. 1)

The table 1 below shows the distribution of urinary infections for each individual haematological malignancy.

Patients identified showed one or more episodes of urinary tract infection as the disease progressed. Figures 2 and 3 show the incidence of such infectious episodes for each gender separately.

Out of the total 253 patients with haematological malignancies undergoing antineoplastic therapy that developed urinary infections, 61.26% were identified as having other associated diseases that could have been a contributing factor for developing an episode of urinary infection: type 2 diabetes mellitus, high blood pressure, association with another type of neoplasia, polycystic kidney, prostate adenoma and adenocarcinoma. Thus, of

<table>
<thead>
<tr>
<th>Primary haematological condition</th>
<th>No. of patients</th>
<th>No. of patients with UTIs</th>
<th>Percentage of UTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple myeloma -MM</td>
<td>97</td>
<td>41</td>
<td>42.26%</td>
</tr>
<tr>
<td>Chronic myeloid leukaemia – CML</td>
<td>74</td>
<td>23</td>
<td>31.08%</td>
</tr>
<tr>
<td>Refractory anemia with blast excess – RABE</td>
<td>54</td>
<td>13</td>
<td>24.07%</td>
</tr>
<tr>
<td>Chronic lymphocytic leukaemia – CLL</td>
<td>232</td>
<td>55</td>
<td>23.7%</td>
</tr>
<tr>
<td>Acute myeloid leukaemia – AML</td>
<td>50</td>
<td>11</td>
<td>22%</td>
</tr>
<tr>
<td>Waldenstrom macroglobulinemia – WM</td>
<td>15</td>
<td>3</td>
<td>20%</td>
</tr>
<tr>
<td>Myeloid metaplasia with myelofibrosis - MMM</td>
<td>16</td>
<td>3</td>
<td>18.75%</td>
</tr>
<tr>
<td>Essential thrombocytemia – ET</td>
<td>61</td>
<td>11</td>
<td>18.03%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma – NHL</td>
<td>331</td>
<td>59</td>
<td>17.82%</td>
</tr>
<tr>
<td>Polycytemia vera – PV</td>
<td>66</td>
<td>11</td>
<td>16.66%</td>
</tr>
<tr>
<td>Hodkin lymphoma – HL</td>
<td>179</td>
<td>22</td>
<td>12.29%</td>
</tr>
<tr>
<td>Acute lymphocytic leukaemia - ALL</td>
<td>19</td>
<td>1</td>
<td>5.26%</td>
</tr>
</tbody>
</table>
the total 145 patients diagnosed with UTI, 25 were hypertensive, 7 were diagnosed with some other co-existing malignant neoplasm, 6 had diabetes mellitus, 6 cases showed co-existence of diabetes and hypertension, and 1 case had polycystic kidney.

Out of the 108 patients diagnosed with UTI, 23 were hypertensive, 16 were known prostate adenoma patients, 8 were diabetic, 5 cases showed co-existence of diabetes and hypertension, 5 patients each had a co-existing neoplasm, and one case was known with
polycystic kidney. Splenectomy was encountered in 5 patients with UTI (4 women and 1 man). (Fig. 5)

The presence of renal calculi was taken into account as a contributing factor for urinary infection: 31 of the 253 patients with UTI had bilateral renal calculi, while 2 had only unilateral renal calculi. 69.69% of these patients (23 cases) with co-existing renal calculi had at least two episodes of UTI.

With regard to the chronic renal disease, the majority of patients haven’t been diagnosed with a pre-existing renal disorder. A total of 83 cases of patients with urinary infections (32.8%) had been diagnosed with chronic renal failure, being at least in stage III of chronic kidney disease (GFR < 60 ml/min/1.73 m^2); the distribution is as follows: 63 patients had a stage three chronic kidney disease, 11 patients – stage four chronic kidney disease (13.25%), and 9 patients had stage five chronic kidney disease (10.84%). (Fig.6)

60.24% of these patients developed at least two episodes of urinary infection as follows: 32 cases had 2 episodes, 13 patients with chronic renal failure - 3 episodes, 3 of these had 4 episodes each, and 1 case each, with five, respectively six episodes of UTI. During episodes of UTI, development of an acute stage of the chronic renal failure was noticed in 38 patients (45.78% out of the 83 with RFG < 60 ml/min/1.73m2).

At the same time, it was noticed that infectious episodes (especially recurrent ones) led to a conclusive decrease of the glomerular filtration rate - and implicitly, aggravation of the stage of the chronic renal disease - in a number of 20 patients, while in a number of 7 patients with chronic renal injury, increases of blood creatinine values were noticed, with a decreased rate of glomerular filtration; however, after the infectious process was stopped, these came back to the initial range, with the patient being in the same stage of the chronic renal disease.

During the urinary infection episodes, levels of blood urea and creatinine increased over the normal range in 50 patients (19.7%) with proper renal function (RFG > 60 ml/min/1.73 m^2).
ml/min/1.73m2), which led to occurrence of episodes of acute kidney injury that recovered after initiation of antibiotic therapy.

As to the pathogen that caused urinary infection, the presence of E. coli was reported in 81% of cases; in 10.2% of UTI, Klebsiella Pneumoniae has been identified; in 5.9% of UTI, Proteus Mirabilis was present; 1.6% cases were caused by Pseudomonas aeruginosa, while the remaining cases were caused by other pathogens: Staphylococcus saprophyticus, Enterobacter, Enterococcus faecalis, Enterococcus species, Acinetobacter.

Novicka and Mroz find that the germs most frequently present in patients with acute leukaemia are Enterobacteriaceae, which is actually similar to non-leukaemia patients. (Novicka and Mroz (15))

DISCUSSION

Looking at the group of 1194 patients diagnosed with hematological malignancies over about seven years, it was noticed that these malignancies affect both genders equally (47.8% women vs. 52.2% men), with no statistically significant difference between their average age (p = 0.4932).

The gender distribution of UTI patients with haematological malignancies show that it is more frequent in women (57.3% vs. 42.7% in men).

Urinary tract infections are complications frequently encountered in these patients, under chemotherapy. They are caused first of all by cytostatic-induced neutropenia and neutropenia induced by bone marrow invasion by malignant cells, but also by co-existing conditions. In this study, the occurrence of urinary infection was detected in 253 patients, which accounts for 21.1% of all cases reviewed; thus, a significant increase in incidence was ascertained, compared to 1-3% occurrence rates in the general population of 1-3%.

A statistically significant higher impairment was identified (p = 0.02) in females (57.3% vs. 42.7%), which could be due to the anatomical peculiarities of the female urinary system (short urethra).

In our study, we used the bacteriological tests (urine cultures) as basic investigation in diagnosing UTI. The UTI diagnosis relied on the presence of significant bacteriuria (>100,000 CFU/ml). We should mention that the other clinical-biological data used in the UTI diagnosis come with a lot of uncertainties, since haematological malignancies may show clinical and biological signs that are similar to UTI signs – such as fever, lumbar pain, inflammatory syndrome, dysuria (bladder impairment during cyclophosphamide therapy, etc.). These would lead to either overdiagnosing or ignoring the UTI. Novicka and Mroz (15) got to the same conclusions and emphasised that diagnosis needs to rely on urine cultures.

In another study on the occurrence of bacteriuria and malignant disease, at the haematological clinic in Sarajevo, Dzirlo-Teodorovic analysed the presence of bacteriuria in such patients and ascertained its presence in 20.65% of the patients. (16) These observations are closely similar to ours – as we identified UTI in 21.1% of the patients with haematological malignancies using urine cultures as the main criterion for diagnosis.

Occurrence of multiple episodes of UTI in the same patient were reported in almost 50% of cases during the evolution of the primary disease. The etiologic agent most frequently identified as producing UTI was E. coli (81% of cases). The other UTI-inducing etiologic agents were: Klebsiella pneumoniae in 10.2% cases, Proteus
mirabilis in 5.9% cases, Pseudomonas aeruginosa in 1.6% cases and other pathogens (Staphylococcus saprophyticus, Enterobacter, Enterococcus faecalis, Enterococcus species, Acinetobacter) in a small percentage (1.1%).

Other authors who analysed UTI in haematological malignancies had similar observations. Thus, Novicka and Mroz (15) analysed bacterial urinary infection in acute leukemia and noticed that the most frequent causes of the urinary infection are various species of gram-negative Enterobacteriaceae, similarly to non-leukemic patients with urinary infection.

Besides neutropenia, the high rates of urinary infectious episodes may be explained by the co-existence of favouring factors: average age 50+, hypertension, diabetes, another neoplasia associated with the haematological disease, prostate adenoma. Among these, hypertension, diabetes mellitus or a combination of them have been identified in a high percentage (28.85%) in these patients. Prostate adenoma was identified in 14.81% of cases. Renal calculi, present in 13.04% of patients with UTI, accounted for the occurrence of recurrent urinary infection episodes in the same patient. In terms of the primary haematological disease, the highest percentage of UTI – 42.26% - was seen in cases of multiple myeloma, explained mostly by the intraluminal obstructive factor resulting from precipitation of myelomatous proteins at tubular level and tubular atrophy.

Regarding other haematological malignancies, high occurrence of UTI is noticed in patients with chronic myeloid leukaemia (31.08%) and chronic lymphocytic leukaemia (23.7%) compared to Hodgkin lymphoma (12.29%) and non-Hodgkin lymphomas (17.82%).

Acute leukaemias show a different occurrence of UTI; thus, acute myeloid leukaemia shows 22% occurrence of UTI, compared to acute lymphocytic leukaemia (5.26%).

Looking at urinary bacterial infections in acute leukaemia, Novicka and Mroz identify such infections in 34% of the patients investigated. They assign this to a decreased response during the inflammatory process, noted in leukemic patients with urinary infection. At the same time, they identify relapses and overinfections in some patients, the latter more frequent in acute lymphoblastic leukemia (Novicka and Mroz) (15).

We too noticed recurrent infections, both in patients with acute leukaemia and in those with other types of haematological malignancies.

They note that, due to non-stable clinical symptoms, multiple changes in the normal laboratory findings in both the urine and the blood occur, which may suggest urinary infection, this should be confirmed by urine culture (Novicka and Mroz) (15).

Actually, our study only discussed UTIs that were confirmed by the presence of significant bacteriuria.

Actually, Dzirlo-Todorovic and al., who analysed patients with malignant haematological disease in a haematological clinic in Sarajevo with regard to UTI, condense their observations to the occurrence of bacteriuria in these patients. They underline the significance of monitoring these patients in terms of the urinary flora, in order to minimise initial infection, relapse and reinfection of the urinary tract (Dzirlo-Todorovic et al) (16).

Another important element of UTI in patients with haematological malignancies is the link with the renal function when the infection occurs.

Thus, UTI sometimes resulted in episodes of acute renal injury or acutisation of a chronic renal injury in a significant number of patients.

Thus, in patients with no prior renal impairment, UTI episodes resulted in increases of creatinine and serum urea above normal values in 19.7% of the patients with UTI and haematological malignancies investigated. The episodes of acute kidney injury recovered after the infectious episode was treated.

We should note that this recovery was not due to the cytostatic therapy administered, which could itself affect kidney function.

In 32.8% of the patients with UTI, the infection occurred on the background of a pre-existing chronic renal disease, leading to acutisation of the chronic kidney injury in a significant percent of patients (45.79%).

Treating the UTI led to improvement in the kidney’s functional impairment.

Actually, the occurrence of the acute kidney injury was also noticed in patients with UTI without haematological malignancies. The recurrent UTI episodes were reported especially in patients with obstructive factors at the level of the urinary tract.

From the discussion above, we notice the following:
- the presence of a haematological malignancy creates favouring conditions for development of UTI, as we mentioned above
- however, UTI, as well as the episodes of kidney function impairment within haematological malignancies could be controlled with appropriate antibiotic therapy.
- UTIs are frequent in patients with haematological malignancies (21.1% of the patients). This can be related to a diminution of the immune anti-infectious capacities in these patients, due to the disease that prevailingly affects the main organs involved in producing immune cells, as well as antibodies. - also, chemotherapy may affect the body’s defence abilities against pathogens - in patients with haematological malignancies, the urinary flora needs to be monitored in order to enable early identification and correct treatment of the UTI. Attention should be given to relapse and reinfection.

REFERENCE: