REZULTATE

Introducere: Boala cronică de rinichi (BCR) poate apare la aproximativ jumătate din cazurile de mielom multiplu, 20% dezvoltând insuficienţă renală. Aceasta poate reprezenta forma de debut a bolii hematologice sau poate apare în cursul evoluției hemopatiei maligne. Obiectiv: Evaluarea BCR la pacienții cu mielom multiplu aflați sub chimioterapie, internați în Clinica de Hematologie a Spitalului Municipal Timișoara pe parcursul a șapte ani, respectiv în perioada ianuarie 2002 – martie 2009. Material și metode: În urma unei analize retro- și prospective, au fost studiați 97 pacienți cu mielom multiplu. Pentru stabilirea gradului de afectare renală s-au urmărit indicii antropometrici, parametrii biologici sangvini și urinari precum și evaluarea factorilor de risc asociați. Rezultate: La debutul hemopatiei, 40,2% din cazuri au prezentat afectare renală, iar dintre aceștia, la 10,25% s-a identificat creșterea stadiului BCR pe parcursul evoluției hemopatiei. Dintre pacienții cu mielom multiplu cu funcție renală inițială bună aflați sub chimioterapie, 12,37% au dezvoltat o boală cronică de rinichi pe perioada urmărită, astfel încât incidența BCR la finalul studiului a fost de 52.58% (p=0.08405). Complicațiile infecțioase urinare cu efect direct renal nu au fost de neglijat, ele fiind prezente la 42,26% din pacienți. Majoritatea celor care au dezvoltat insuficiența renală cronică (83,33%) au primit scheme chimioterapice complexe. Concluzie: Mielomul multiplu reprezintă una din cauzele de afectare renală atât prin acțiune directă la nivel tubular cât și datorită asocierii factorilor de risc (de tipul proteinuriei, hipercalcemiei, hiperuricemiei, deshidratării, complicațiilor infecțioase, hiperviscosității și a comorbidităților (în special HTA și factorul obstructiv), peste care se suprapune terapia antineoplazică cu potențial nefrotoxic cert.

ABSTRACT

Introduction: The chronic renal disease (CRD) can occur in approximately half of the multiple myeloma cases, with 20% of them developing renal failure. It may represent the onset of the haematological disease, or may appear during the progress of the malignant haemopathy. Objective: To evaluate the chronic renal disease in multiple myeloma patients undergoing chemotherapy, admitted in the Haematology Clinic of the Timisoara Municipal Hospital over a period of seven years, from January 2002 to March 2009. Material and methods: Following retrospective and prospective evaluation, we examined 97 multiple myeloma patients. We established the level of renal impairment based on anthropometric indices, blood and urine biological parameters, and the evaluation of associated risk factors. Results: At the onset of the haemopathy, 40.2% of the cases displayed renal impairment, with the stage of the chronic renal disease advancing in 10.25% of these cases. Among multiple myeloma patients undergoing chemotherapy and having good initial renal function, 12.37% developed chronic renal disease over the period we monitored; thus, the incidence rate of the CRD at the end of the study was 52.58% (p = 0.08405). Urinary infectious complications with direct renal effect were also quite significant, occurring in 42.26% of patients. The majority of patients who developed chronic renal failure (83.33%) received complex schemes of cytostatic therapy. Conclusion: Multiple myeloma is one of the causes of renal impairment, both through direct action at tubular level, and due to an association of risk factors (such as proteinuria, hypercalcemia, hyperuricemia, dehydration, infectious complications, hyperviscosity) and co-existing pathologies (especially HTA and obstructive factor), combined with antineoplastic therapy having an established nephrotoxic potential.

Key Words: chronic renal disease, multiple myeloma, myelomatous kidney, chemotherapy
it affects the elderly in general. Incidence rates in Europe are 5.72/100,000 population, with approximately 27,500 new cases discovered every year.1

The myeloma-associated nephropathy is polymorphous. The chronic renal disease is seen in approximately half of the multiple myeloma cases, with 20% of the cases developing renal failure. Up to 50% of the newly diagnosed patients display decreased creatinine clearance, and approximately 9% require dialysis due to severe deterioration of the renal function.

Renal failure can be a form of onset of the haematological disease, or it can develop during the evolution of the malignant haemopathy. In general, renal impairment is the result of tubular obstruction by hyaline cylinders made of protein material, atrophy and consecutive interstitial fibrosis (myelomatous kidney).2 Proteinuria is characteristic, but usually does not exceed 3 grams/24 hours. Approximately 10% of patients develop nephrotic syndrome.

Renal amyloidosis is present in 15-30% of the multiple myeloma patients, with proteinuria being the most frequent renal manifestation at onset, identified in ~80% of the patients. Nephrotic syndrome is found in 30-50% of the renal amyloidosis cases, while chronic renal failure occurs in 70% of the patients.

Goldschmidt and Lannert claim that approximately 20% of the multiple myeloma patients have renal failure at the onset of the haematological disease, but the condition is reversible in half of the cases, by elimination or diminution of some of the aggravating factors.1

Thus, the pathogenesis of the chronic renal disease in multiple myeloma occurs through a number of mechanisms.65 The precipitation of light chains (that are produced in excess in patients with this haemopathy, compared to levels in healthy people) at the level of the renal tubes, resulting in formation of obstructive cylinders, leads to breaking of the basement membrane and consecutive interstitial fibrosis. Thus, urine tests point out a monoclonal proteinuria with Bence Jones light chains. When in large amounts, these chains disturb the renal function, either by massive precipitation in the tubes, leading to cylinder formation (myeloma cast nephropathy), or by direct toxic action on the proximal tubes. The nephrotoxic potential of the Bence Jones protein was outlined in experimental studies conducted on mice.67 The myelomatous kidney was the object of research in studies conducted by many authors.6-19 It is a specific renal impairment, characterized by the presence of intra-tubular cylinders with a protein structure made of light monoclonal chains, glomerular ultra-filtrates and the Tamm-Horsfall protein.

In 25% of the cases, the chronic renal disease in multiple myeloma can also be induced by sedimentation of monoclonal immunoglobulins, with subsequent thickening of the renal tubes’ basement membrane, leading to glomerulosclerotic lesions. Cases of rapidly progressive and membranoproliferative glomerulonephritis were also reported.5,20-22

The cellular and humoral immune dysfunction results in increased susceptibility to infections - a factor with negative impact on the already impaired renal function; at the same time, the immune suppression from the corticotherapy and cytostatic therapy increases the risk of infections.23 These can lead to the occurrence of acute renal failure episodes that can aggravate the chronic renal disease and implicitly deteriorate the body. Thus, some authors recommend prophylactic antibiotic treatment to prevent infections in multiple myeloma.24

Chemotherapy used in treating malignant haemopathies can have a nephrotoxic effect. Antineoplastic therapy can be nephrotoxic and lead to renal failure by impairment at tissue, interstitial and - rarely - glomerular level, as well as through mechanisms that affect circulation at kidney level. The presence of the chronic renal disease in a multiple myeloma patient can favor the toxic action of cytostatic medication.25-27 Methotrexate - an antagonistic anti-metabolite of folic acid - has a nephrotoxic effect, as it precipitates at the level of the distal tube, already impaired in the multiple myeloma and the consecutive renal failure. Nephrotoxicity depends on the dose and duration of the treatment and is favored by dehydration.28-30 Cyclophosphamide can determine severe haemorrhagic cystitis and – in rare cases – renal tubular necrosis. The literature mentions cases of renal failure after administration of melphalan, which more frequently induces cystitis and urination perturbations. Carmustine (a derivate of nitrosourea) is potentially nephrotoxic, as it induces complex renal lesions, such as tube atrophy and interstitial fibrosis. Evolution to chronic stages may generate glomerulosclerotic lesions.26-28,30,32

Most patients require treatment for chemotherapy in various schemes: CVP (cyclophosphamide, vincristine and prednisone) and VAD (vincristine, doxorubicin and dexamethazone). Some studies underline the beneficial role of VAD on kidney damage in multiple myeloma.31

MATERIAL AND METHODS

Following retrospective and prospective evaluation, we identified 97 multiple myeloma patients admitted at the Haematology Clinic of
These patients received complex cytostatic therapy with nephrotoxic potential: CVP (cyclophosphamide, vincristine and prednisone) associated with melphalan. The remaining patients with initial proteinuria received varying therapy schemes.

Increased susceptibility to infections showed in the high percent of cases with urinary infections. Infectious episodes at the level of the urinary tract were seen in 41 patients (42.26%), with more than half of them (25 patients) having recurrent urinary infections. We ascertained that in 60% of the cases these recurrences happened in the context of a pre-existing renal condition, in patients with GFR<60 ml/min/1.73m², while in 5 patients (20%) these infectious episodes played a significant part in the subsequent development of chronic renal disease. The distribution of multiple myeloma patients per number of urinary infection episodes is given in Table 1.

Table 1. Distribution of MM patients per number of UTI episodes.

<table>
<thead>
<tr>
<th>No. of urinary infection episodes</th>
<th>No. patients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 episode</td>
<td>16</td>
<td>39.02%</td>
</tr>
<tr>
<td>2 episodes</td>
<td>17</td>
<td>41.46%</td>
</tr>
<tr>
<td>3 episodes</td>
<td>5</td>
<td>12.19%</td>
</tr>
<tr>
<td>4 episodes</td>
<td>1</td>
<td>2.44%</td>
</tr>
<tr>
<td>5 episodes</td>
<td>1</td>
<td>2.44%</td>
</tr>
<tr>
<td>6 episodes</td>
<td>1</td>
<td>2.44%</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>100%</td>
</tr>
</tbody>
</table>

In terms of the pathogen triggering the urinary tract infections, *E. Coli* was the most frequent (87.8%); *Kleb. Pneumoniae* was identified in urine culture in 3 patients (7.31%), and *Proteus mirabilis* and *Ps. aeruginosa* shared the same incidence rate (2.44%).

Figure 1 shows the distribution of the presence of *E. Coli* in urine cultures in patients with multiple myeloma and urinary tract infections, compared to other pathogens.

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The 97 multiple myeloma patients examined from January 2002 to March 2009 displayed the following distribution per age and gender: 50 patients (51.54%) were female, aged 34 – 79 (with the average age being 60.64 +/- 11.88 years) and 47 patients were male (48.45%), aged 42 – 82 (with the average age being 65.43 +/- 9.17 years).

Among them, 73.19% (71 cases) had various co-existing pathologies: 31 patients had high blood pressure, 4 were diabetics, 5 cases had high blood pressure and diabetes, 4 had another associated neoplasm, 6 patients were known with chronic viral hepatitis, 3 men were diagnosed with prostate adenoma, and the others had coronary disease. 7.21% (7 patients) were known with unilateral or bilateral kidney lithiasis.

Hyperuricemia was detected in 24 cases (24.74%) at first admission, but none of them displayed associated lithiasis.

When the haematological disease was diagnosed, proteinuria was present in 44.32% of the myeloma patients (43 cases), out of which 32 were known with renal impairment, GFR<60 ml/min/1.73m². Two patients with initial proteinuria and no previous renal impairment developed the chronic renal disease during the monitored period. Both patients were hypertensive and repeatedly developed infectious complications – urinary and other – with consecutive renal failure.
In terms of the chronic renal disease, 39 cases (40.2%) had renal impairment at the onset of the haemopathy, with GFR<60 ml/min/1.73m². A number of 24 patients (61.53%) were found with chronic renal disease stage III; 11 patients (28.2%) were in stage IV, and 4 cases in stage V. (Table 2)

Table 2. Distribution of patients with MM and renal impairment per stages of the CRD.

<table>
<thead>
<tr>
<th>Stage of CRD</th>
<th>Number of patients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage III</td>
<td>24</td>
<td>61.53%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>11</td>
<td>28.2%</td>
</tr>
<tr>
<td>Stage V</td>
<td>4</td>
<td>10.25%</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>100%</td>
</tr>
</tbody>
</table>

The following observations were made regarding these multiple myeloma patients with chronic renal disease already formed at the time when they came to the Haematology Clinic: 3 patients were diagnosed with chronic glomerulopathy. Renal biopsy has revealed one case of renal amyloidosis with significant proteinuria, consecutive nephrotic syndrome and chronic renal failure. In two other situations, renal biopsy has revealed membranoproliferative glomerulonephritic lesions (in one patient) and myeloma cast nephropathy (in the second case).

The patients’ dynamics showed that most of them remained at the initial stage of the CRD; only in 4 cases (10.25%) there was a permanent decrease of the glomerular filtration rate—with implicit advancement of the chronic renal disease stage. We noticed that none of these patients displayed any obstructive factors; half of them were diagnosed with recurrent urinary infections and all of them had aggravations of the pre-existing renal disease in the context of existing infections, which led to an aggravation of the renal impairment. In terms of chemotherapy schemes these patients were following, they were all on cyclophosphamide, vincristine, melphalane and prednisone.

Among multiple myeloma patients under chemotherapy who previously had GFR>60 ml/min/1.73m², 12 cases (12.37%) developed chronic renal disease during the monitored period. While evaluating the presence of risk factors in these patients and of the infectious complications they developed, as well as the chemotherapy scheme applied, we noticed the following: 5 patients had high blood pressure and one had another co-existing neoplasm, and the obstructive factor (renal lithiasis) was present in 3 patients. We also noted that only two patients had proteinuria at the moment of receiving the multiple myeloma diagnosis, and hyperuricemia was present in 5 cases. Regarding urinary infection episodes in these patients, 7 had recurrent urinary tract infections, with consecutive acute renal failure in almost half of the cases (3 patients – 42.85%). In terms of therapy, 2 patients were on melphalane, 7 were treated with complex schemes including melphalane, cyclophosphamide, vincristine and prednisone, one was on carmustine in a VBAP scheme (vincristine, carmustine, Adriamycin and prednisone), and 2 were on the VAD scheme (vincristine, Adriamycin and dexamethasone).

At the end of the study, the chronic renal disease was present in 52.57% of the cases (51 patients). Figure 2 shows a graphic comparison between the incidence rates of the chronic renal disease in this lot at the beginning and at the end of the study; the difference is not statistically significant (p=0.08405).

Out of the 97 multiple myeloma patients examined, 7 (7.21%) died during the study period. This was due to infectious complications occurred in 3 patients with good renal function, but who developed episodes of irreversible acute renal failure, and in 4 cases with previously impaired renal function (1 case was in stage III of the chronic renal disease, 2 cases were in stage IV and one in stage V) and aggravation of the chronic renal failure.

DISCUSSIONS

Unlike in some studies claiming that the renal chronic disease is seen in 20% of the cases at the onset of the haematological disease (Goldschmidt and Lannert), in this study renal impairment was present in 40.2% of the patients at the time the patients were diagnosed with multiple myeloma.

Compared to previous studies regarding the incidence of chronic renal disease in multiple myeloma, claiming that CRD is found in approximately half of the patients, the incidence rates of renal impairment we found at the end of our study were similar (52.57%).

Within the lot we studied, we identified one case
of membranoproliferative glomerulonephritis, one case of myeloma cast nephropathy and one case of renal amyloidosis with nephrotic syndrome that had an unfavorable development.

Urinary infectious complications with direct effect on the renal function by induction of acute renal failure episodes, subsequently recovered through adequate therapeutic behavior, were quite significant. As much as 42.26% of the myeloma patients were diagnosed with urinary tract infections, and more than half of these (60.97%) had recurrent urinary infections.

The majority of patients who developed chronic renal failure (83.33%) were under complex cytostatic therapy schemes including melphalane, cyclophosphamide, vincristine, carmustine, Adriamycin and prednisone.

**CONCLUSION**

From the data presented above, multiple myeloma is revealed to be one of the cases of renal impairment, both through a direct action following the organic changes induced at tube level, and through association of risk factors (such as proteinuria, hypercalcemia, hyperuricemia, dehydration, infectious complications, hyerviscosity), co-existing pathologies (especially high blood pressure and obstructive factor) and antineoplastic therapy with established nephrotoxic potential.

**REFERENCES**