New Methods in Treatment of Renal failure in Patients with Multiple Myeloma: A Review with Immunological Approach

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Abstract

Multiple myeloma (MM), as one of a variety of autoimmune diseases, affects the immune system and, on the other hand, is considered to be a hematologic impairment. One of the most common and important complications of MM is renal impairment (RI), which is associated with an increase in serum Cr levels. Although RI is one of the major complications of MM, the routine therapies for MM patients practically lack acceptable efficacy for the improvement of RI patients, and as a result, RI remains a deadly disease with high mortality rate and very bad prognosis; therefore, new treatments have been proposed for the improvement of nephropathy in patients with MM, and extensive research is ongoing in various phases, including clinical trials. Attempts were made in this study to review common and advanced treatments (immuno-therapy, cell therapy, new therapies based on genetic engineering) in these patients and to consider this disease from an immunological viewpoint.

Key words: Multiple myeloma, renal impairment, Immunomodulatory drugs

Introduction

The immune system is the body's natural defense against infection and malignant diseases. However, sometimes its responses can cause autoimmune diseases (1-7). Multiple Myeloma (MM) is one types of autoimmune diseases associated with B cells and plasma cells are highly proliferated and IgG antibody is produced at high levels in serum and urine. It alone accounts for 10% of all hematologic malignancies. The disease affects people's immune system and, is also considered as a hematological defect. The disease mainly involves the elderly (8) so that the average age of people involved with MM is 65 years (9). This disease is more common in men and the prevalence of this disease in Africa and the United States is twice as high as in Europe. One of the most common and important complications of MM is renal impairment (RI), which is associated with an increase in serum creatinine levels. RI is seen in 20-40% of patients newly diagnosed with MM (NDMM) and 25% of patients (RRMM) and / or refractory multiple myeloma with relapsed symptoms and creatinine levels increases to above 4 mg/ml in most people with this condition (10). MM begins with acute kidney injury (AKI), and recurrence is associated with nephropathy casts.

Prevalence of RI in patients with MM

RI is seen in half of the patients with MM. Severe RI is also seen in more than 15% of these patients. Table 1 presents the prevalence of all types of disorders involved in this disease.

Today for prevention and treatment most disorders such as urinary system dysfunctions have been evaluated and new drugs and methods and their outcomes have been considered (11-19). Since routine therapies for patients with MM have virtually no acceptable efficacy for the improvement of RI patients and RI is still considered as a disease with high mortality and very bad prognosis; new treatments have been proposed for the improvement of nephropathy in patients with MM. In this study, attempts were made to review common and advanced treatments (immunotherapy, -cell therapy and new therapies based on genetic engineering) and discuss this disease from an immunological viewpoint.

Mechanisms of nephropathy symptoms in patients with MM

Renal damages in patients with MM mostly occur due to the toxic effect of the free light chain (FLC). Light chains are proteins produced by plasma cells. Within a plasma cell, two light chains and two heavy chains are combined to form an immunoglobulin. The free light chain is filtered through the glomeruli and is removed and catabolized by the cells of the proximal tubule cells (PTCs). The FLC level in the serum of patients with MM can be increased up to 100 times, which indicates the high ability of PTCs cells in absorbing and catabolizing these proteins, which, as a result of increased activity of these cells, leads to an increase in the concentration of FLC in the urine and fluid in the tubule of the kidney(20). Urinary FLC has a high affinity for binding to the carbohydrate portion of (THP), which causes aggregates that cause cysts and blockage of renal tubules(21). FLC can activate inflammatory pathways and cause fibrosis in the tubular area during inflammation in cells in the tubule (20). Also, various factors, including nonsteroidal anti-inflammatory compounds, dehydration, acidosis, and angiotensin converting enzyme (ACE) inhibitors interfere with the onset of RI and contribute to the nephropathy caused by FLC. On the other hand, factors like hypercalcium may further aggravate the symptoms of nephropathy (10, 22, 23)(Figure 1).

MM therapies

1. Common MM Therapies:

1-1 Primary Care Support

In case of transient but recurrent defects in the kidney, especially in people who excrete plenty of Bence Jones protein, immediate supportive treatments have been taken for patients for whom combination of bortezomib and dexamethasone is a good therapeutic option. And in limited cases, thalidomide is also prescribed. Lenalidomide is another low-dose drug that can control and treat the symptoms of nephropathy in patients with MM(24). In addition, plasma replacement has been suggested as a treatment for nephropathy in patients with MM. However, the use of this treatment is controversial in RI people suffering from excretion of Bence Jones protein.

1-2. Corticosteroids (dexamethasone) and conventional chemotherapy

Dexamethasone is one of the cortical derivatives that plays an important role in improving nephropathy in patients with MM. A high dose of dexamethasone leads to a higher rate of kidney regeneration activity in MM patients who have recently suffered RI. It is also prescribed, independently of dialysis, for patients with kidney complications and high risk of severe proteinuria, which discharges Bence Jones at high levels in the urine (25). In addition, the new drug combination of thalidomide+bortezomib is safe in the treatment of nephropathy in patients with MM, leading to renal function improvement. However, the use of dexamethasone and chemotherapy is recommended for effective treatment of nephropathy in these individuals (25-27).

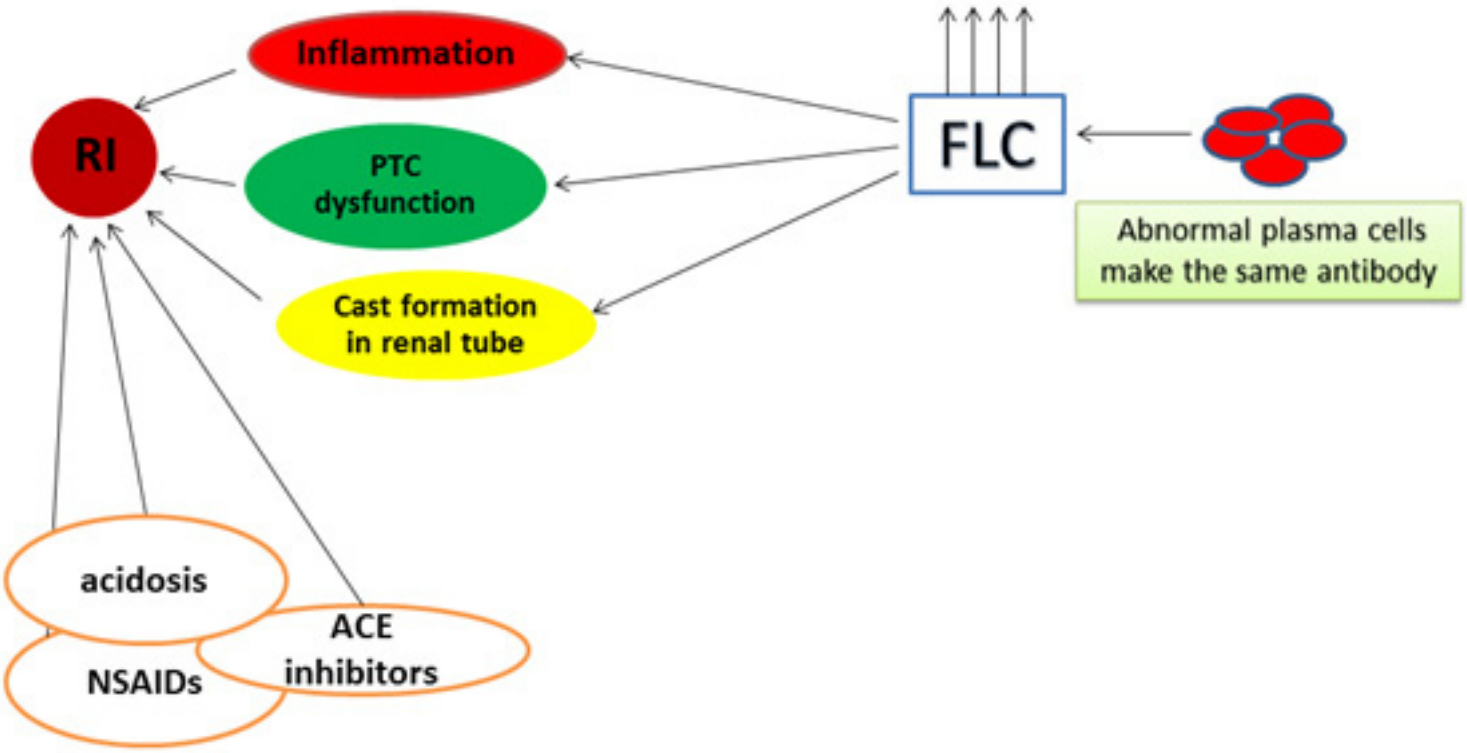
2. New treatments and advanced drugs:

Over the last decade, there has been a major advance in MM treatment and new and advanced therapies were later used for the treatment of transplant recipients as well as those who were not eligible for transplantation (28) and considering their effectiveness, the probability of complete responses (CR), progression of disease, disease-free survival (PFS) and total survival (OS) have been increased. Combined therapeutic approaches, including dietary regimens and chemotherapy, have been proposed as a standard treatment approach, which can be done in both the ASCT patients as well as patients who do not intend organ transplants(29). The new therapeutic approaches and advanced drugs that are introduced and presented in this effort are presented in more detail as follows.

Table 1: Prevalence of some types of defects and RI in patients with MM

Disorders	Prevalence
Severe kidney failure	More than 15% of patients
High blood pressure	60-80% of patients
The need for dialysis	2-4% of patients
Renal impairment (RI) in patients with relapsing-remitting or refractory MM	25% of patients
Early death Risk in patients with severe renal failure	12% of patients

Figure 1: Mechanisms involved in RI-caused MM



Renal impairment: RI; Free light chain: FLC; Proximal tubule cells = PTCs; Angiotensin converting enzyme: ACE.

Table 2: New anti- MM drugs the mechanism of action of which is proteasome inhibition

Drug name	Group owned	Efficacy in RI Patients	Mechanism	Combined therapy	Reference
Bortezomib	Proteasome inhibitors	Gold standard for the treatment of RI in patients with MM	Bortezomib inhibits the 26S portion of the proteasome	Bortezomib along with thalidomide and lenalidomide	(30-32)
Carfilzomib	Proteasome inhibitors (2nd generation)	An effective drug in treating nephropathy of patients who have already received at least two therapies	Proteasome inhibition and apoptosis stimulation	Combination with lenalidomide and dexamethasone and only dexamethasone for RRMM patients	(33-35)
Ixazomib	Proteasome inhibitors	Increasing overall response rate (78% instead of 72%), progression free surviving and response period (mean 21 to 15) in patients with MM	Selectively and reversibly inhibits the β5 unit of proteasome, which is part of the proteasome 20S subunit.	Dexamethasone and other drugs	(36-38)

2.1 Proteasome inhibitors

Proteasome inhibitors have been able to significantly advance the progression of MM disease independently of organ transplants. Some of the new anti-MM drugs, the mechanism of action of which is proteasome inhibition are listed in Table 2 (previous page).

2-2 Immunomodulatory drugs

Immunomodulatory drugs (IMiDS) directly affect multiple myeloma cells and bone marrow environments, leading to changes in cytokines, inhibition of angiogenesis, and increased number and function of various cells, including T, NK, and NKT. IMiDs are also capable of replicating Treg cells. In addition, IMiDs can enhance the ADCC defense response in NK cells by increasing expression of FasL and granzymes. Considering this feature, IMiDs can be used in targeted therapies for immunotherapy(39). As indicated in the mechanism section, inflammatory response is one of the effective factors in the progression and treatment process. Therefore, this group of drugs can effectively and potentially contribute to the treatment of MM patients (Table 3). Given that immunomodulators include a wide range of therapeutic strategies, some of the most recent and most important ones are mentioned here, and some of them are listed in Table 3.

2-2-1 - Bispecific T cell engages (Bi-TEs)

BiTEs are a novel immunotherapy approach in relation to antibodies and T cells. This method enables us to design antibodies using genetic engineering, which is in contrast to the usual dual specificity. For example, the antibody is designed in such a way that, on the one hand, as a specific marker of T lymphocytes for CD3 and as a specific marker for CD19 on the surface of the cells of the lymphoma, on the other hand. Thus, a tumor cell with T lymphocyte (as the main anti-tumor cell) will be placed next to each other, resulting in the destruction of tumor cells at higher intensity. BiTEs have been investigated for the treatment of melanoma in vitro and in vivo and satisfactory results were also obtained.

2-2-2 Adoptive T cell Therapies (ACT)

In this method, the T-cell of a person with MM is isolated from its whole blood, and these cells lead to the activation and development of T-cells in the presence of anti-CD3-CD28 beads and IL2 in the ex-vivo environment and after being discharged from the bone marrow from the myeloid line and the autologous transplantation, this ex-vivo amplified compound is inoculated and leads to primary lymphocytosis. Recently, this method has also been used for the first time in the production of bone marrow infiltrated t lymphocytes (mILs) as clinical anti-tumor immunity (40). The results of this treatment are satisfactory, but more confirmation is needed in this regard.

2-2-3 TCR transgenic T cells

In this method, TCR infusion occurs with high affinity and common peptide antigens between two types of cancer (NY-ESO-1, LAGE-1)(41). Initial laboratory tests indicate that the infusion T cell, the function of which is actively maintained, occurs and these cells remain active in the body and in the presence of IL2 without fatigue for up to one year. On the other hand, all people with MM are being treated to respond to HLA-dependent treatment. Nevertheless, these cells are HLA-dependent and therefore, this is a therapeutic constraint compared to the CART method(25).

2-2-4 BTK inhibitors

Bruton Tyrosine kinase is an enzyme from the Tec family that is expressed in hematopoietic cells such as B and myeloid cells, mast cells, and platelets, and plays a key role in several important cellular processes, including differentiation, proliferation, cell migration and apoptosis(42, 43). In the case of mutation in the BTK gene, the maturation of these cells is impaired and genetic and hereditary diseases such as XLA (X-linked gamma-globulinemia) are created(44). On the other hand, the excessive activity of BTK refers to the neoplasm associated with B cells(45). Ibrutinib is one of the drugs produced in this field and is capable of inhibiting the function of this enzyme during the binding of covalent to BTK and its administration alone or in combination with other drugs can provide satisfactory therapeutic results. In a study in 2015, a combination of Ibrutinib and Carfilzomib with or without dexamethasone was used to treat RRMM patients and a target response rate of 62% was reported(46). The effect of BTK expression in the treatment of the disease is so important that there are many solutions to inhibit the expression of this enzyme, which can have a significant effect on the treatment process.

2-3- Monoclonal Antibodies

Therapies performed based on monoclonal antibodies against target antigen have been defeated due to the lack of clear expression of the target molecule on the plasma cells. In fact, early studies have only shown the minimal activity of anti-CD20, which is expressed in 20% of plasma cells. Studies have also been conducted on several other monoclonal antibodies (anti [TRAIL-R1, IL6, CD38, CD138, CD74, CS1, CD56, IGF-1R, CD40]), among which two monoclonal antibodies, Elotuzumab and Daratuzumab, is important and practical in MM disease (Table 4). In addition, B cell maturation antigen (BCMA) antibodies are under construction and its clinical trial is in progress. BCMA, a superfamily protein TNFR, is used as an important target in the construction of monoclonal antibodies and can be of great help in treating patients with MM. On the other hand, the production of antibodies against CD138, CD56 and CD74 is also under investigation in the early stages of clinical practice (25).

2-4 High-dose therapy and autologous stem cell transplantation (HDT & ASCT)

ASCT (Post-autologous Stem Cell Transplant Therapy) is one of the supportive therapies that is used for MM patients during a 12-month period (63-66), leading to improved OS and better treatment outcomes) during the transplantation process. The ASCT method is applicable to all eligible MM patients. In this therapeutic approach, following a stem cell transplant, 3-4 courses of the drug regimen, including bortezomib and dexamethasone in combination

Table 3: Some immunomodulatory drugs for the treatment of multiple myeloma

Drug name	Category	Mechanism of action	Combined with other drugs	Efficacy	Reference
Thalidomide	Immunomodulatory drugs			Satisfactory outcomes have been obtained using thalidomide compared with biosamide and some other drugs in the treatment of RRMM individuals.	(47, 48)
Lenalidomide	Immunomodulatory		Administration of lenalidomide with high doses of dexamethasone	The use of lenalidomide in the treatment of severe nephropathy is under investigation	(49)
Pomalidomide	Immunomodulatory	The production of other cytokines and increasing IL2, IL10 and IFNγ, and also reducing IL6, directly inhibits the growth and development of tumor cells.	Combined with low dose dexamethasone	Approved by the FDA and used in treating nephropathy in RRMM individuals.	(50-53)
Panobinostat	Immunomodulatory	The histone deacetylases enzyme inhibitor results in the apoptosis of malignant cells from different pathways.	Combined with anticancer drugs like bortezomib and dexamethasone		(54, 55)

Table 4: Monoclonal antibodies approved by the FDA for patients with MM

Antibody name	Target	Mechanism of action	Reference
Elotuzumab	Anti-CS1 (SLAMF7) antibody	It can kill myeloma cells through antibody-dependent cytotoxicity (ADCC).	(56-58)
Daratuzumab	Anti-CD38 antibody	Antibody during binding to CD38 causes apoptosis of the cell by complement or antibody-dependent cytotoxicity. Also performed ADCP (Antibody Dependent Phagocytosis) activity.	(59-62)

with lenalidomide, thalidomide, or cyclophosphamide, is received by the patient(67). The administration of this therapeutic approach helps patients maintain their condition for a progressive free survival (PFS)(68, 69). In addition, bortezomib's mechanism of action, which is to inhibit proteasome, helps to create better PFS in MM patients with intermediate and high-risk; however, the post-ASCT administration of this drug compared with thalidomide, which has toxic effects in the blood, offers better treatment outcomes. Since the relapse of the disease occurs almost entirely in MM patients, the relapse period can be changed from 2.5 years to 4 years (70, 71).

2.5 Plasma exchange

The kappa and lambda chains of FLC, which have a molecular weight of 45KD and 22.5KD, respectively, are excreted from the renal glomeruli after a half-life of 3 and 6 hours. Consequently, anti-myeloma effects are induced in individuals through the "plasma replacement" and FLC levels are also reduced. Interestingly, patients who receive this treatment are protected against other kidney injuries that may occur in the future (72). Additionally, the combination of plasma replacement therapy with bortezomib-based therapies gives rise to strong responses in all NDMM and RRMM patients (73). Plasma replacement in the short term leads to the purification of proteins in the extravascular part, but in any case, the plasma replacement in the long run leads to the purification of other essential proteins; therefore, the use of membranes have cut-off for higher molecular weight proteins, can be a remedy in this case (74).

2.6 Renal transplantation

One of the treatment methods for MM patients involved with RI is renal transplantation, which can be used as a treatment alternative for these patients, due to the increasing number of patients. The results of a study which was conducted on 166 patients in 2013 showed that the risks of immunosuppression should be considered in those who received ASCT and kidney allograft transplants, and eventually 26 of them survived without the need for dialysis (10, 75).

2.7 Histone deacetylases (HDACs)

HDACs deacetylates lysine residues (tails) in both histone and non-histone proteins. This enzyme in the chromatin structure creates a local relaxation and regulates the specific expression of the gene. HDACs acts nonspecifically and can deacetylate non-histone proteins that is also intended to alter the activity and sustainability of their activity, so the inhibitory effect of this enzyme complex on the treatment of multiple myeloma is very important (76) and specifically the combination of inhibitors of HDACs and proteasome or immunomodulatory drugs play a very important role in the progression of this disease in pre-clinic and clinical phases. However, clinical studies that are performed using selective HDACs inhibitors reduce the side effects of treatment, which leads to increased tolerance in patients and has no negative effect on the multiple myeloma activity; therefore satisfactory outcomes were obtained when this treatment was performed (77). Panobinostat is a deacetylase inhibitor that can produce better treatment outcomes in combination with dexamethasone and bortezomib. Inhibiting HDACs activity leads to an increase in acetylated histone proteins, as a result of this epigenetic change, eventually during the formation of the chromatin regimen results in the activation of the transcriptional process in individuals (78, 79). Vorinostat is another oral deacetylase inhibitor that is effective in treating cutaneous T-cell lymphoma (CTCL) (80). Therefore, both panobinostat and vorinostat are involved during the inhibition of deacetylation in treatment of multiple myeloma. The panobinostat is so important in the treatment of these patients that it is prescribed in combination with dexamethasone and bortezomib for RRMM patients who have received at least two therapy y lines in the past (80, 81)and have shown resistance and this therapeutic pattern was approved by the FDA in February 2015.

Conclusion

Multiple myeloma is a hematologic malignancy that alone accounts for 10% of all hematologic malignancies. One of the main complications of the disease, which is seriously problematic, is high mortality and a lack of satisfactory effect of the common treatments intended for this group of patients. So, in the last decade, extensive researches and studies have been carried out to produce new drugs; therefore, many drugs could help with the treatment of patients with multiple myeloma by obtaining approval from the FDA. Meanwhile, drugs that affect the immune system of the human body, namely immunotherapies, are extremely important.

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