

Efficacy of “Pomalidomide” Containing Polychemotherapy Regimens in the Treatment of Relapsed Forms of Multiple Myeloma

Gulchekhra Makhamadaliyeva^{1,*}, Khamid Karimov², Abdurakhmon Kaumov³

¹Clinical Hematology Department, Republican Specialized Scientific-Practical Medical Center of Hematology MoH RUZ, Tashkent, Uzbekistan

²Department of Molecular Medicine and Cell Technologies, Republican Specialized Scientific-Practical Medical Center of Hematology MoH RUZ, Tashkent, Uzbekistan

³Administration, Republican Specialized Scientific-Practical Medical Center of Hematology MoH RUZ, Tashkent, Uzbekistan

Abstract The presented article is devoted to the issues of clinical efficacy and safety, the specifics of the practical use of pomalidomide in patients with recurrent multiple myeloma. The article presents the results of the main clinical studies of pomalidomide-containing Pd and PVD treatment programs in treated patients with a diagnosis of multiple myeloma in RSSPMC of Hematology. The effectiveness of treatment regimens for recurrent MM based on pomalidomide is discussed.

Keywords Multiple myeloma, Recurrent multiple myeloma, Pomalidomide, Dexamethasone

1. Introduction

Relevance. Multiple myeloma (MM) is the 2nd most frequently detected oncohematological pathology, accounting for about 10% of blood system tumors [1,6]. Despite the successes achieved in recent years in the treatment of MM and the increase in overall survival, the disease is considered incurable and is characterized by alternating remissions and relapses. The use of new drugs, including immunomodulatory drugs (lenalidomide, pomalidomide), has increased overall survival from 3 years to 7-10 years or more, but the 10-year survival rate does not exceed 17%. “Pomalidomide”, an analog of the drug “Thalidomide”, was approved by the FDA on February 8, 2013 [1,2,5,8]. According to the literature [1,4,8,10], the drug is more effective than “Thalidomide” and “Lenalidomide” and is a more potent 3rd generation IMiDs, which has an antiproliferative effect on tumor plasma cells. Immunomodulatory effect of the drug is realized by reducing the activity of regulatory T-lymphocytes and inhibiting the production of proinflammatory cytokines by monocytes: TNF-alpha and IL-6 [3,4,7,9]. According to Votyakov O.M. that the main target of the drug “Pomalidomide” is a protein - Cereblon. “Pomalidomide” binds to this target and inhibits the activity of ubiquitinligase, is also an inhibitor of COX2 transcription. In addition, due to anti-angiogenic and anti-inflammatory action “Pomalidomide” promotes

reprogramming of the microenvironment. The synergistic effect of the combination of “Pomalidomide” with the drug “Dexamethasone” seems to be important for clinical practice [8,10]. Since MM is characterized by a chronic course, the search for new treatment protocols at each subsequent relapse of the disease is critical to increase overall survival.

2. Main Body

2.1. Purpose of the Study

Evaluate the efficacy of "Pomalidomide" containing polychemotherapy regimens in the treatment of relapsing forms of multiple myeloma.

2.2. Material and Methods of Investigation

In "Republican specialized scientific-practical medical center of Hematology of MH RUZ" the analysis of the results of using pomalidomide containing treatment programs Pd ("Pomalidomide"/ "Dexamethasone"), PVD ("Pomalidomide"/ "Bortezomib"/ "Dexamethasone") in treated patients with the diagnosis of Multiple Myeloma was carried out.

Thirty-six patients with reliably diagnosed multiple myeloma aged 34 to 72 years were examined, including 22 women (61%) and 14 men (39%). The largest number of patients were women aged over 60 years.

We treated 36 patients with relapsed course of Multiple Myeloma who were resistant to 1,2 line of therapy, 10 of them were patients with dialysis-dependent myeloma nephropathy.

* Corresponding author:

alteam2201@gmail.com (Gulchekhra Makhamadaliyeva)

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The median time from diagnosis to patient inclusion in follow-up was 16 months (7 months to 32 months).

The effectiveness of multiple myeloma treatment was evaluated according to international criteria [2,7] based on the assessment of laboratory parameters after each course of therapy (indices of general blood analysis, bone marrow, blood biochemical analysis, immunochemical study of monoclonal immunoglobulins) and further once every three months.

The immunochemical method was used to determine the type and amount of immunoglobulin heavy (IgG, A and rare types) and light chains (κ , λ) and free chains (κ , λ) in blood serum by immunofixation of pathological monoclonal immunoglobulin and electrophoresis was determined with the help of the automated system "InterlabPretty" (Interlab, Italy) using reagents of the same company before treatment, after each course and after 3 courses of therapy (Fig. 1).



Figure 1. Semi-automatic device for electrophoresis of blood plasma proteins "Interlab Pretty"

Table 1. Separation of patients according to the investigated criteria

Parameters		Group 1	Group 2
Median age		57.6±6.1	62.2±3,5
Sex	Male	9	7
	female	13	7
ECOG status		1	1
Immunochemical variant of myeloma			
IgG		14	10
IgA		2	2
With the secretion of Bence Jones protein		5	1
Other		1	1
Durie-Salmon staging			
IIIA		16	5
IIIB		6	9
Median prior lines of therapy			
Proteasome inhibitors (bortezomib)		20	14
Immunomodulators (lenalidomide)		22	14
Autotransplantation of hematopoietic stem cells		1	5
Dialysis-dependent nephropathy		7	3

Group 1 - group 22 patients (Pd) in whom "Pomalidomide" - used at a dose of 4 mgx1 times /day on days 1-21) and "Dexamethasone" (20 mg on days 1, 8, 15 and 22) every 28

days were used.

Group 2 14 patients (PVd program approved by the EMA in 2019) received:

"Pomalidomide" at a dose of 4 mgx1 times /day on days 1-21, "Bortezomib" 1.3 mg/m² on days 1, 4, 8 and 11 and "Dexamethasone" (20 mg on days 1, 4, 8 and 11) every 28 days (table 1).

2.3. Results and Discussion

Clinical examination of patients after therapy in both subgroups showed a significant decrease in the percentage and intensity of ossalgia, infectious complications and extramedullary manifestations. No new pathologic fractures were observed among the patients. At the same time, improvement of renal function in MM patients was noted.

The PVd group showed a higher incidence of neutropenia (22% vs. 7%), infections (20% vs. 8%), and peripheral sensory neuropathy (9% vs. 1%) than the Pd group (Fig. 2).

The average amount of total protein before treatment in patients with stage IIIA MM was 98,6±5,5 g/l (p<0,001), and in patients with stage IIIB the index averaged 98,9±5,8 g/l (p<0,001). At the same time the comparative analysis of the quantity of this index in patients with group I (92,7±5,5 g/l; p<0,001) and group II (100,3±5,7 g/l; p<0,001) showed some difference consisting in its increase in 1,08 times in group II patients. The study of platelet level after treatment in different immunochemical variants of MM allowed to note positive dynamics of this index in relation to the values before treatment. Thus, in "II" group the level of platelets exceeded that before IgG κ treatment in 1.1 (169,3±13,2 X 10⁹/l vs. 157,3±11,1 X 10⁹/l; p>0,05), in IgG λ - significantly in 1.5 (201,3±22,1 X 10⁹/l vs. 134,3±15,0 X 10⁹/l; p<0.01), at IgA κ - in 1.4 (198.5±7.1 X 10⁹/l vs. 143.3±26.6 X 10⁹/l; p<0.05), at IgA λ - in 1.8 (193.5±24.4 X 10⁹/l vs. 107.2±18.5 X 10⁹/l; p<0.05), which is probably associated with persisting depression of plateletopoiesis after exposure to PVd polychemotherapy. It was noted that positive dynamics after treatment with regard to hemoglobin and erythrocyte levels was associated with improvement of the state of medullary hematopoiesis, which was most effective in patients of group "II".

A complete response was achieved in 3 x (8.3%) patients after 3 courses of PVd. OHCA was obtained in 9(25%) patients (PVd-6 patients, Pd-3), CHO-11(30.6%) patients (PVd-3 patients, Pd-8) and disease stabilization was recorded in 2(Pd) x patients. Disease progression was observed in 6 patients on the background of "Pomalidomide" containing PCT programs.

The overall response rate with pomalidomide-containing programs was 69.4% (according to the world literature - 38-86%). In 5 patients therapy was discontinued due to the development of allergic reaction in the form of urticaria.

The results of the studies showed good tolerability of pomalidomide, the main manifestations of toxicity were manageable myelosuppression, non-hematologic complications were controllable, and no life-threatening side effects such as liver damage, diarrhea, or nausea were observed (Fig. 3).

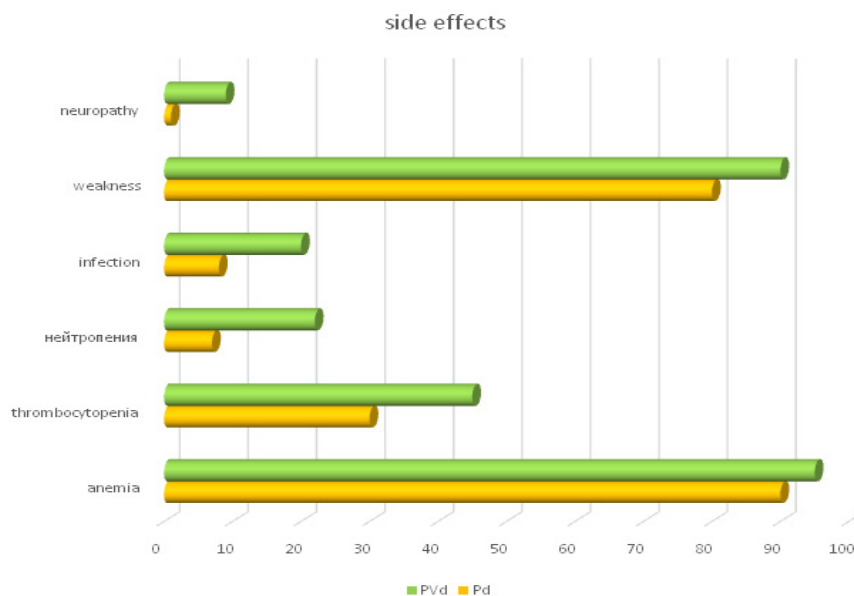


Figure 2. Side effects of therapy in the studied groups

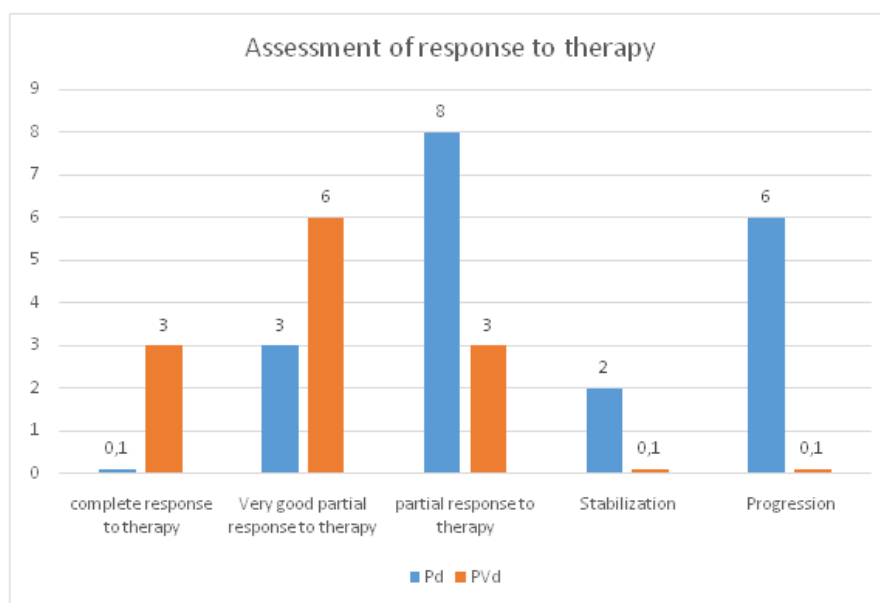


Figure 3. Degree of response to therapy for multiple myeloma in the study groups

3. Conclusions

Summarizing the above data, we can conclude that the treatment performed in both groups indicates improvement of both clinical and laboratory status of MM patients. However, the dynamics of the studied clinical and laboratory parameters after treatment in the "II" subgroup was characterized by the greatest recovery in comparison with the "I" group, which was expressed clinically in the disappearance of characteristic symptoms of MM, laboratory greater increase in hemoglobin, and platelets, the greatest decrease in the level of total protein, microglobulins. All this directly convincingly proves the great effectiveness of PVd protocol application. It can be concluded that the use of pomalidomide-containing programs in patients with relapsing multiple

myeloma showed high efficacy.

This drug can be recommended for patients with multiple myeloma, including those with advanced renal failure. Polychemotherapy according to the PVd protocol consisting of bortezomib, pomalidomide and dexamethasone is effective compared to the Pd protocol. Further studies to determine the role of pomalidomide in the treatment of patients not only with relapsed MM, but also in patients with newly diagnosed myeloma.

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