Original Article
A comparison of the efficacy and safety of ixazomib and lenalidomide combined with dexamethasone in the treatment of multiple myeloma

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Abstract: Objective: To explore the efficacy and safety of ixazomib and lenalidomide combined with dexamethasone (DXMS) in the treatment of multiple myeloma (MM). Methods: A total of 80 patients with newly diagnosed MM were randomly divided into the ID group (ixazomib + DXMS, n=40) and the RD group (lenalidomide + DXMS, n=40). All patients were given DXMS orally on the 1st, 8th, 15th, and 22nd day of the treatment cycle (20 mg each time). The patients in the ID group also received 4 mg of ixazomib citrate capsules orally on the 1st, 8th, and 15th day of the treatment cycle, whereas those in the RD group received 25 mg of lenalidomide capsules orally from the 1st to the 21st day of the treatment cycle continuously. The primary outcome measure was progression-free survival (PFS) within 5 years, and the secondary outcome measures were overall survival (OS), overall response rate (ORR), quality of life, and safety. Results: The median PFS and median OS in the ID group were similar to those in the RD group (30.03 and 50.21 months vs. 25.04 and 46.33 months, both P>0.05). The ID group had higher complete remission rate (13 cases vs. 5 cases, P<0.05), but similar ORR compared with the RD group (90.00% vs. 82.50%, P>0.05). After treatment, the pain intensity assessed by Numeric Rating Scale and the functional impairment measured by Karnofsky Performance Status Scale of the two groups were both relieved (both P<0.001), and no intergroup differences in these two markers were observed (both P>0.05). The incidence of grade 1-2 peripheral neuropathy in the ID group was higher than that in the RD group (30.00% vs. 20.00%, P=0.032). There were no differences in other adverse reactions between the two groups (all P>0.05). Conclusion: Compared with the combination of lenalidomide and DXMS, ixazomib combined with DXMS can achieve higher complete remission rate and more improved PFS and OS in patients with newly diagnosed MM, which is a safe and effective method.

Keywords: Ixazomib, lenalidomide, multiple myeloma, remission rate, safety

Introduction

Multiple myeloma (MM) is characterized by malignant clonal proliferation of bone marrow plasma cells and is considered to be an incurable disease [1]. The disease can lead to damage of target organs, renal function, and bone structure [2]. MM has a high prevalence in elderly people. As the elderly patients often have heart and kidney diseases, immune deficiency, and other problems, the patients usually cannot tolerate traditional chemotherapy. Although chemotherapy can completely relieve the symptoms of some patients, there is still a possibility of recurrence of the disease [3].

At present, the application of autologous stem cell transplantation combined with high-dose chemotherapy as well as the application of more advanced treatment support therapies, immunomodulatory drugs, and proteasome inhibitors have improved the first-line treatment of MM patients and helped saving patients’ lives [4-6]. So far, the only way to cure MM is hematopoietic stem cell transplantation, but due to factors such as financial difficulties and the advanced age of the patients, this treatment is difficult to be carried out. At present, most of the treatments for MM are just to relieve symptoms and prolong the survival period of patients. However, how to prolong the survival period, delay and prevent recurrence of MM, and avoid immunosuppression need to be further investigated [7]. As a result, finding an effective treatment method with low toxicity for
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MM patients has become an essential and urgent research topic clinically.

Low-dose glucocorticoids can inhibit inflammatory factors and transcription factors, thereby inducing apoptosis of MM cells. When low-dose glucocorticoid is used in combination with proteasome inhibitors (PI), the therapy can achieve marked outcome in treating MM [8, 9]. Bortezomib, as a first-generation PI, can improve the treatment efficacy for MM as well as prolonging the survival period of patients. However, the long-term safety and tolerability of bortezomib have been questioned [10]. Ixazomib is an oral boric acid peptide PI, which shows great advantages in improving the route of administration, reducing toxic reactions, and overcoming drug resistance [11, 12]. Lenalidomide, as a second-generation immunomodulatory drug, can inhibit proliferation and induce apoptosis of tumor cells by inhibiting angiogenesis, activating and improving immune response, cellular immunity, and tumor-killing function, improving bone marrow microenvironment, and promoting the synthesis of various anti-tumor cytokines [13-15]. At present, studies on ixazomib versus lenalidomide combined with DXMS for treating MM are rare. Therefore, in the present study, we aimed to explore the efficacy and safety of ixazomib and lenalidomide combined with DXMS in the treatment of MM.

Materials and methods

Participants

A total of 80 patients with first-episode MM treated in our hospital from January 2014 to December 2015 were selected for this study.

Inclusion criteria: 1) Patients who met the diagnostic criteria of MM defined by the International Myeloma Working Group [16]. 2) Patients aged between 18 and 65 years with complete clinical data of general information and therapeutic efficacy; 3) Patients had full consciousness, could have accurate communication, and could cooperate with the examinations; 4) Patients who had no abnormalities in other organs; 5) Patients who had not been treated with ixazomib or lenalidomide in the past.

Exclusion criteria: 1) patients were sick with light-chain amyloidosis leukemia and plasma cell leukemia; 2) creatinine clearance rate was no more than 30 mL/min, and absolute count of neutrophil and platelet in blood routine examination were no more than 1×10^9/L and 75×10^9/L, respectively; 3) patients who had contraindications or intolerance to the therapeutic drugs used in this study.

The ethics committee of our hospital approved this project. All the patients signed informed consent. The patients were divided into the ID group and the RD group of 40 each using the random number table method.

Methods

In this study, 28 days were defined as one treatment cycle. The patients in the ID group were given ixazomib citrate capsules (Ninlaro, H20180010) combined with DXMS (Huanan Pharma, China). Ixazomib citrate capsule was taken orally at a dose of 4 mg on the 1st, 8th, and 15th day of the treatment cycle. The patients in the RD group were treated with lenalidomide capsules (Revlimid, H20171348) combined with DXMS. The lenalidomide capsule was taken orally at a dose of 25 mg from the 1st to the 21st day of the treatment cycle continuously. The patients in the two groups received DXMS orally on the 1st, 8th, 15th, and 22nd day of the treatment cycle (20 mg each time and once a day). The two groups were compared and analyzed after two treatment cycles.

Outcome measures

The primary outcome measure was progression-free survival (PFS) within 5 years, and the secondary outcome measures included remission rate, overall survival (OS), quality of life, and incidence of adverse events.

The myelogram was reexamined at the end of the second treatment cycle to assess the disease remission. EBMT/ABMTR standard was adopted for evaluation [17]. Complete remission (CR) was defined as the following: plasmacytoma disappeared completely in soft tissues, the number of bone marrow plasma cells was no more than 5%, and M-protein immunofixation electrophoresis was negative. If the M-proteins in plasma decreased by more than 90%, the remission was considered as very good partial remission (VGPR). If the M-proteins
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Table 1. Baseline data in the two groups (X ± sd, n, %)

<table>
<thead>
<tr>
<th>Item</th>
<th>ID Group (n=40)</th>
<th>RD Group (n=40)</th>
<th>χ²/t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female, n)</td>
<td>23/17</td>
<td>27/13</td>
<td>0.853</td>
<td>0.356</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.9±11.4</td>
<td>63.3±10.9</td>
<td>0.860</td>
<td>0.393</td>
</tr>
<tr>
<td>Immunofixation electrophoresis (n)</td>
<td></td>
<td></td>
<td>0.172</td>
<td>0.583</td>
</tr>
<tr>
<td>IgG type</td>
<td>15</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgA type</td>
<td>13</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light chain type</td>
<td>12</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-ISS staging (n)</td>
<td></td>
<td></td>
<td>0.554</td>
<td>0.758</td>
</tr>
<tr>
<td>Stage I</td>
<td>18</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>14</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>8</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogenetic risk stratification* (n)</td>
<td></td>
<td></td>
<td>0.220</td>
<td>0.639</td>
</tr>
<tr>
<td>Standard risk</td>
<td>25</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>15</td>
<td>13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: *Detected by fluorescence in situ hybridization, high-risk cytogenetic types include: del (17p), t (4;14), and t (14;16). R-ISS: revised international staging system.

Statistical analysis

SPSS 23.0 was used to analyze the data. Count data are expressed as number or percentage and was tested by χ² test or Fisher’s exact test. Measurement data are expressed as mean ± standard deviation (X ± sd). Independent sample t-test was used for inter-group comparison, and paired samples t-test was used for intra-group before-and-after comparison. The test was two-tailed at a significance level of α=0.05. The PFS and OS survival curves were plotted and compared by the Log-rank test.

Results

Baseline data

There were no differences in the baseline data between the two groups (all P>0.05). See Table 1.

Remission in the two groups

There was no difference in ORR between the ID and the RD groups (90.00% vs. 82.50%, χ²=0.949, P=0.330). However, the CR rate in the ID group was higher than that in the RD group (χ²=4.588, P=0.032). See Table 2.

PFS and OS in the two groups

The ID group had a higher median PFS than the RD group (30.03 months vs. 25.04 months), in plasma decreased by 50%, the remission was considered as partial remission (PR). If the M-proteins in plasma decreased by 25%, the remission was defined as minor remission (MR). A decrease of less than 25% in the proportion of M-proteins in plasma indicated stable disease (SD), whereas an increase of M-proteins by no less than 10 g/L, or an increase of bone marrow plasma cells proportion by no less than 25%, or occurrence of a new lesion indicated progressive disease (PD).

The overall response rate (ORR) = (sum number of PR, VGPR, CR)/total number of cases ×100%.

After treatment, disease progression and death were recorded in both groups to assess OS and PFS. The median follow-up period was 4.5 (3.8-5) years, and the follow-up ended in December 2019.

The numerical rating scale (NRS) and Karnofsky Performance Status Scale (KPS) were used to evaluate patients’ quality of life. The NRS score ranged from 0 to 10 points with a higher score indicating a greater level of pain [14]. The KPS score was positively correlated with the health status of patients. Patients with a KPS score higher than 80 were considered to have independence in activities of daily living; patients with a score between 50 and 70 were considered to require partial assistance in daily activities; patients with a score less than 50 points were considered to be unable to care for themselves and require the assistance of others [11].

The incidence of adverse reactions in the two groups was observed, including adverse reactions of blood (anemia, neutropenia, lymphocytopenia, and thrombocytopenia), adverse reactions of the digestive tract (nausea, vomiting, diarrhea, and dyspepsia), and other adverse reactions (peripheral neuropathy, rash, constipation, fatigue, etc.). The adverse events were classified according to Common Toxicity Criteria 5.0 by the National Cancer Institute [18].
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Table 2. Remission of patients in the two groups (n, %)

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>CR</th>
<th>VGPR</th>
<th>PR</th>
<th>MR</th>
<th>SD</th>
<th>PD</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID Group</td>
<td>40</td>
<td>13</td>
<td>12</td>
<td>11</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>90.00</td>
</tr>
<tr>
<td>RD Group</td>
<td>40</td>
<td>5</td>
<td>10</td>
<td>18</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>82.50</td>
</tr>
</tbody>
</table>

χ² = 4.588, P = 0.032

Note: CR: complete remission; VGPR: very good partial remission; PR: partial remission; MR: minor remission; SD: stable disease; PD: progressive disease; ORR: overall response rate.

Figure 1. Survival curves of PFS and OS in the two groups. A: PFS within 5 years in the two groups; B: OS period in the two groups. PFS: progression-free survival; OS: overall survival.

Figure 2. NRS and KPS scores in the two groups before and after treatment. A: NRS scores; B: KPS scores. Compared with pre-treatment, ***P<0.001. NRS: numerical rating scale; KPS: Karnofsky Performance Status Scale.

There were no intergroup differences in the NRS and KPS scores before treatment (both P>0.05). After treatment, the NRS scores decreased and KPS scores increased in both groups (all P<0.001), but there were still no differences between the ID group and the RD group in these two markers (both P>0.05). See Table 3 and Figure 2.

Incidences of adverse reactions in the two groups

The main blood adverse reactions in the ID and the RD groups were anemia (32.50% vs. 30.00%), thrombocytopenia (30.00% vs. 32.50%), and lymphocytopenia (47.50% vs. 40.00%), and the reactions were mostly in grade 1 and 2. No intergroup differences were observed in the incidences of the adverse reactions (all P>0.05). There was no peripheral neuropathy in grade 3 or higher in the ID group and the RD group. The incidence of grade 1-2 peripheral neuropathy in the ID group was higher than that in the RD group (30.0% vs. 20.00%, P=0.032). Incidences of fatigue (mainly grade 1) were high in both groups without an intergroup difference (70.00% vs. 65.00%, P>0.05). Other common adverse reac-
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Table 4. Occurrence of adverse reactions in the two groups (n, %)

<table>
<thead>
<tr>
<th>Item</th>
<th>ID group (n=40)</th>
<th></th>
<th></th>
<th></th>
<th>RD group (n=40)</th>
<th></th>
<th></th>
<th></th>
<th>( \chi^2 )</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Level 1-2</td>
<td>Level 3-4</td>
<td>Total</td>
<td>Level 1-2</td>
<td>Level 3-4</td>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hematologic toxicities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>12</td>
<td>1</td>
<td>13 (32.50)</td>
<td>11</td>
<td>1</td>
<td>12 (30.00)</td>
<td>0.058</td>
<td>0.809</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10</td>
<td>0</td>
<td>10 (25.00)</td>
<td>9</td>
<td>0</td>
<td>9 (22.50)</td>
<td>0.069</td>
<td>0.793</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11</td>
<td>1</td>
<td>12 (30.00)</td>
<td>13</td>
<td>0</td>
<td>13 (32.50)</td>
<td>0.058</td>
<td>0.809</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>16</td>
<td>3</td>
<td>19 (47.50)</td>
<td>14</td>
<td>2</td>
<td>16 (40.00)</td>
<td>0.457</td>
<td>0.499</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse reactions of digestive tract</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>0</td>
<td>5 (12.50)</td>
<td>3</td>
<td>0</td>
<td>3 (7.50)</td>
<td>0.556</td>
<td>0.456</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>0</td>
<td>3 (7.50)</td>
<td>3</td>
<td>0</td>
<td>3 (7.50)</td>
<td>1.000</td>
<td>0.363</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7</td>
<td>1</td>
<td>8 (20.00)</td>
<td>5</td>
<td>0</td>
<td>5 (12.50)</td>
<td>0.827</td>
<td>0.363</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7</td>
<td>0</td>
<td>7 (17.50)</td>
<td>6</td>
<td>0</td>
<td>6 (15.00)</td>
<td>0.092</td>
<td>0.762</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other adverse reactions</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>12</td>
<td>0</td>
<td>12 (30.00)</td>
<td>8</td>
<td>0</td>
<td>8 (20.00)</td>
<td>4.588</td>
<td>0.032</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>8</td>
<td>0</td>
<td>8 (20.00)</td>
<td>5</td>
<td>0</td>
<td>5 (12.50)</td>
<td>0.827</td>
<td>0.363</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>28</td>
<td>0</td>
<td>28 (70.00)</td>
<td>26</td>
<td>0</td>
<td>26 (65.00)</td>
<td>0.228</td>
<td>0.663</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>7</td>
<td>0</td>
<td>7 (17.50)</td>
<td>8</td>
<td>0</td>
<td>8 (20.00)</td>
<td>0.082</td>
<td>0.775</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: *Comparison of total incidence of AEs between Id group and Rd group; # Using Fisher’s exact test.

In recent years, the novel drug, lenalidomide, has shown marked efficacy in the treatment of MM [19]. The combination of lenalidomide and DXMS has been recommended for the treatment of refractory MM by the NCCN Guidelines for Multiple Myeloma [20]. Spina et al. believed that lenalidomide can achieve good outcome in the treatment of recurrent MM, especially for patients who had recurrence after allogeneic hematopoietic stem cell transplantation, and lenalidomide can be used as a long-term therapy for the remission [21]. Spina et al. carried out two cycles of RD treatment (enalidomide + DXMS) among 104 patients with recent MM, and the ORR of the patients reached 73%, showing marked outcome [21]. Rajkumar et al. treated 34 MM patients with RD regimen, and the ORR was 91% [22]. In this study, the ORR of the RD group was 82.5%, which was between the ORR of the above two studies.

Proteasome is a complex protease synthesized in the cell, which can regulate the level of proteins in the cells, thereby maintaining the stability of the intracellular environment [23]. Ixazomib mainly achieves the treatment effect by selectively inhibiting the 20S proteasome [24]. Compared with bortezomib (the first-generation proteasome inhibitor), ixazomib can be administered orally, which is more convenient to use. Moreover, ixazomib has a shorter dissociation half-life of protease, stronger ability to penetrate the tissues, higher enrichment in tumor tissue, and can induce apoptosis of drug-resistant cell lines, thus achieving better anti-MM effect than bortezomib [23, 24]. Clinical studies have proven that ixazomib alone or ixazomib combined with other drugs can achieve satisfactory results in treating MM patients [25-27]. Krishnan et al. treated 32 patients with refractory MM with the ID regimen. The results of the phase I/II clinical trials showed that cases of PR + VGPR accounted for 48%, SD accounted for 76%, the median PFS was 8.6 months, and the 1-year OS was 82% [25]. In a study by Kumar et al. on the ID regimen for refractory MM, the ORR reached 64% in patients ≥65 years old after 2 treatment cycles, and PFS reached 18.7 months which was improved significantly, revealing that ixazomide combined with DXMS has great clinical value for treating MM [26]. Another study showed that ixazomib combined with DXMS can also achieve a good outcome in treating incipient MM; the ORR of patients could reach 71%, and the clinical treatment effect could be increased with the increase of...
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the treatment cycles [27]. In our study, the ORR in the ID group reached 90%, and the median PFS (30 months) and OS (50.21 months) were much higher compared with those in the previous studies [25-27]. The number of CR cases in the ID group was higher than that in the RD group (13 cases vs. 5 cases). Compared with pre-treatment, the NRS and KPS scores of the two groups also improved markedly, suggesting that both the ID regimen and RD regimen are effective in improving the quality of life of Chinese patients with MM. Also, ID regimen as an oral regimen is convenient to apply and has high patient compliance and satisfaction.

Patients with MM can be affected by both cancer cells and chemotherapy drugs, which can damage the body function and cause a series of severe stress reactions. Since the elderly patients often have weakened body functions and low immunity, they are more vulnerable to tumor and chemotherapy toxicity. Therefore, it is important to select a treatment method that has a low impact on the physical function of patients. Previous studies have shown that RD regimen can enhance the anti-myeloma effect but can cause various adverse reactions. In a study by Moreau et al., the researchers switched to ixazomib monotherapy for maintenance after using the RD regimen for 12 consecutive treatment cycles [28]. Although their results showed high ORR (80%) and CR + VGPR (63%), 86% of the patients had adverse events over grade 3 during treatment and 52% had severe adverse events. Thrombocytopenia, neutropenia, gastrointestinal disorders, and peripheral neuropathy were common adverse events reported in their treatment. Kumar et al. also pointed out that the adverse events over grade 3 in the MM treatment with lenalidomide and ixazomib mainly include rash, peripheral neuropathy, thrombocytopenia, neutropenia, and an increase of blood glucose level [29]. During the follow-up in this study, no patients stopped treatment due to severe adverse events. The main blood adverse reactions were anemia, thrombocytopenia, and lymphopenia, which were mostly in grade 1-2, and there were no significant differences between the two groups. There was no peripheral neuropathy of grade 3 or above in the two groups, but the incidence of grade 1-2 peripheral neuropathy in the ID group was significantly higher than that in the RD group. Other grade 1-2 adverse events included nausea, diarrhea and rash, which were common during the treatment. After symptomatic support treatment, the adverse reactions were all relieved, suggesting that the two treatment regimens are safe and can be tolerated by patients.

The results of this study demonstrated that ixazomib has good safety in the treatment of MM. However, the long-term efficacy and safety of ixazomib need to be confirmed by clinical studies with longer follow-up time and larger sample size. In addition, we only conducted a comparative study of drugs in patients with incipient MM and did not include patients with refractory or relapsed MM. The response and tolerance of these patients to ixazomib-based treatment need to be further evaluated.

To sum up, compared with the combination of lenalidomide and DXMS, ixazomib combined with DXMS can achieve a higher proportion of CR and more improved PFS and OS in patients with newly diagnosed MM, which is a safe and effective method that can be recommended for clinical application.

Disclosure of conflict of interest

None.

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