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Application of ixazomib monotherapy and combination therapy in patients with multiple myeloma

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Abstract: In the past few decades, the survival rate of patients with multiple myeloma has improved significantly. This improvement is mainly due to the development of proteasome inhibitors and immunomodulatory drugs, which are the cornerstone of the treatment of multiple myeloma. Ixazomib is a selective and reversible proteasome inhibitor. It can be used as a single agent or combined with other immunomodulators to treat multiple myeloma. This article mainly reviews the effectiveness and safety evaluation of ixazomib monotherapy and its combination therapy in patients with multiple myeloma prospected.

Keywords: Multiple Myeloma; Ixazomib; Safety; Effectiveness

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1. Summary of multiple myeloma

Multiple myeloma is a kind of rare progressive hematological malignancy[1]. There are about 86,000 new cases of multiple myeloma in the world, accounting for 13% of all hematological malignancies, 1% of all them are the newly diagnosed cancers and 2% of cancer-related deaths[2]. The characteristic manifestation of multiple myeloma is the clonal accumulation of plasma cells in bone marrow[1]. Due to the presence of monoclonal immunoglobulin and bone marrow plasma cell infiltration in the serum or urine of patients, patients often have pain, fracture, swelling, pathological manifestations of bone degradation osteolytic changes. Although there are proteasome inhibitors and immunomodulators and other related drugs, up to now, multiple myeloma is an incurable disease, which is characterized by multiple relapses, and most cases need multi-line treatment[3]. In addition, compared with the general mm patients, the initial diagnosis is in the late stage of the disease[4], high risk cytogenetic abnormalities[5], regardless elderly or frail patients[6, 7]. The prognosis of the group was very poor. Therefore, both newly diagnosed and relapsed patients with multiple myeloma still need to expand and optimize the existing treatment options and treatment strategies.

2. Mechanism of proteasome inhibitors

One of the basis of the diagnosis of multiple myeloma is the presence of myeloma cells in vivo. Myeloma cells produce abnormal immunoglobulin, which leads to the increase of proteasome activity. Proteasome activity plays an important role in regulating intracellular protein turnover and maintaining intracellular homeostasis. Proteasome inhibitors destroy protein turnover and protein accumulation, leading to cell death. Ixazomib is the first proteasome inhibitor approved for the treatment of multiple myeloma. So far, bortezomib is considered as the standard treatment from first-line treatment to relapse in patients with myeloma. However, patients with bortezomib are prone to peripheral neuropathy, and can not reduce the incidence of adverse reactions by changing the way it is used. In the past two years, two new proteasome inhibitors, carfilzomib and ixazomib, have been developed. Carfilzomib is an irreversible proteasome inhibitor of epoxidone, which is administered intravenously six times per cycle. There is a risk of cardiovascular events (hypertension, heart failure) and renal events (such as renal failure). Ixazomib is a selective and reversible proteasome inhibitor, which can be used alone or in combination with other immunomodulators in the treatment of multiple myeloma. Ixazomib can be administered orally, which greatly improves the patient's compliance.

Proteasome is a complex of multi catalytic enzymes involved in the degradation of intracellular proteins[8]. Compared with normal cells, tumor cells are more dependent on proteasome pathway to remove degraded proteins[9]. Therefore, it is more susceptible to proteasome inhibition. As a proteasome inhibitor, isazomib can inhibit chymotrypsin like activity of B5 subunit of 20S proteasome and preferentially bind to and inhibit chymotrypsin like protein hydrolysis sites, thus

inducing apoptosis of multiple myeloma cells. Ixazomib is the first and only oral proteasome inhibitor approved for the treatment of multiple myeloma in the world. The recommended regimen of ixazomib combined with lenalidomide and dexamethasone is 4mg of ixazomib on days 1, 8 and 15, 25mg of lenalidomide on days 1 to 21, and 40mg of dexamethasone on days 1, 8, 15 and 22 during the 28 day treatment cycle until disease progression or unacceptable toxicity occurs. If toxicity occurs, or patients with liver or kidney damage, reduce the dose of ixazomib.Ixazomib can be swallowed with water. In order not to affect the metabolism of the drug, it is forbidden to eat any food at least 2 hours before and at least 1 hour after taking medicine[10].

3. Efficacy of ixazomib in the treatment of multiple myeloma

3.1 Application of ixazomib monotherapy and combination therapy in newly diagnosed patients with multiple myeloma

According to the standard IRD (ixazomib, lenalidomide, dexamethasone) regimen, 64th and 65th patients with newly diagnosed multiple myeloma were included in the first two clinical trials to study the application of ixazomib in newly diagnosed multiple myeloma. The data showed that the objective remission rates were 88% and 94% respectively according to the standard IRD (ixazomib, lenalidomide, dexamethasone) regimen. Among them, 58% and 68% of patients had excellent partial remission, and the progression free time was 35.4 months and 24.9 months, respectively. After complete remission, 32% and 22% of patients received ixazomib monotherapy[11-13]. IRD regimen (ixazomib, lenalidomide, dexamethasone) is also considered to be the first choice of induction therapy before autologous hematopoietic stem cell transplantation and consolidation therapy after transplantation in patients with newly diagnosed and newly treated multiple myeloma who meet the conditions of transplantation. Ixazomib can also be used as a single drug maintenance treatment. Preliminary data showed that the response to ixazomib was deepened in each stage of treatment. The estimated 2-year progression free time and overall survival were 83% and 95% respectively[14].

3.2 Application of ixazomib monotherapy and combination therapy in patients with relapsed and refractory multiple myeloma

For relapsed and refractory patients, Richardson et al. Evaluated the efficacy of ixazomib. The study showed that in 50 patients with evaluable response, nearly 15% of patients achieved vgpr or above, and about 76% achieved partial remission and disease stability[15]. In a clinical trial conducted by Kumar et al., 70 patients with multiple myeloma were included in the study. The patients were randomly divided into 4mg ixazomib group and 5.5mg ixazomib group. Among the 30 patients with PR or above, 9 cases were in the 4mg group and 16 cases in the 5.5mg group. The 1-year survival rate was 96% and the PFS was 8.4 months[16]. In the double-blind ixazomib phase III clinical trial, 722 patients with multiple myeloma were randomly assigned to IRD (ixazomib, lenalidomide, dexamethasone) group and XRD (placebo, lenalidomide, dexamethasone) group. The efficacy data showed that the median duration of efficacy in the ixazomib group was significantly better than that in the placebo group (20.6 months: 14.7 months). The objective response rate and excellent partial response rate in the ixazomib group were higher than those in the placebo group (78%: 72% and 48%: 39%, respectively). The median response time was 1.1 and 1.9 months in the ixazomib group and 1.9 months in the placebo group, 20.5 months in the ixazomib group and 15.0 months in the placebo group[17]. In patients with high-risk cytogenetic multiple myeloma, the efficacy of ixazomib is very significant. In the tomarine-mm1 study, of 552 patients with cytogenetic data, 137 (25%) had high-risk cytogenetics (fish showed deletion of 17p, t (4; 14) or T (14; 16)). In this cohort, the median time to progression (PFS) was 21.4 months in the IRD group and 9.7 months in the XRD (placebo, lenalidomide, dexamethasone) group[18]. In a phase 112 clinical trial (nct02206425) study, ixazomib was used instead of bortezomib or carfilzomib in the treatment of multiple myeloma patients who failed to respond to the combination regimen. The other drugs in the combination therapy were the same as the previous treatment. The study showed that in patients with multiple myeloma who had completed at least one cycle (n = 37), the median follow-up time was 1.6 months. When the dose of ixazomib was 3 mg (n = 21), Orr was 0%, and 43% of patients were in stable state. In the second stage, when the dose of ixazomib was 4 mg (n = 16), Orr increased to 19%, and 43% of patients remained stable[19]. It can be seen that for patients with relapsed and refractory multiple myeloma, ixazomib can stabilize the state of the disease, at least can make the disease no longer progress or the degree of progress is slower than before.

3.3 Application of ixazomib monotherapy and combination therapy in patients with

maintenance medication

For patients who have achieved complete remission, the use of ixazomib for maintenance treatment will prolong the disease-free time of patients.In the tourmaline-mm3 team phase III clinical trial study[20]. In 2 years after complete remission, 656 patients were randomly divided into two groups, ixazomib maintenance group (n = 395) or placebo maintenance treatment group (n = 261) on the first, eighth and 15th days of the 28 day cycle. At a median follow-up of 31 months (27.3-35.7 months), the data showed that the risk of disease progression was reduced by 28% (median progression free time 26.5 months vs 21.3 months). Compared with placebo (8 cases, 3%), patients treated with ixazomib were not more likely to develop a second malignancy (12 cases, 3%). For the patients after hematopoietic stem cell transplantation, although hematopoietic stem cell transplantation prolongs the disease-free time and overall survival rate of patients with multiple myeloma, most patients will eventually relapse. The application of 2-year ixazomib maintenance treatment after transplantation can significantly improve the disease-free time, reduce adverse drug reactions, and ensure a higher quality of life.

4. Efficacy of ixazomib in the treatment of multiple myeloma

In terms of the safety of ixazomib, the results of phase I clinical trial showed that bortezomib untreated group was more prone to adverse drug reactions than bortezomib refractory group. The most common adverse events were nausea (42%), thrombocytopenia (42%), fatigue (40%) and rash (40%) when the dose of ixazomib was 2.0mgg/m^2. 12% of patients had grade 112 peripheral neuropathy, but no grade 334 peripheral neuropathy. When the dose of ixazomib was 2.23 mggm2, the adverse reactions were grade 3 rash and grade 4 thrombocytopenia[15]. In the phase II clinical trial, patients with multiple myeloma were randomly divided into ixazomib group (medication: ixazomib, lenalidomide, dexamethasone) and placebo group (medication: placebo, lenalidomide, dexamethasone). The data showed that the elderly had a higher probability of adverse events[21]. In the study of phase I and II clinical trials, the addition of ixazomib to RD (lenalidomide, dexamethasone) did not seem to significantly increase the adverse reactions of patients. 98% of patients in the ixazomib group and 99% of the placebo group had adverse events of any level, that is, the physical discomfort caused by the drug. The incidence of grade 3 or above adverse events in IRD group was only slightly higher than that in placebo group. The main reason was that the incidence of thrombocytopenia in IRD group was higher than that in placebo group. The incidence of grade 4 adverse events (18% in the ixazomib group: 15% in the placebo group), serious adverse events (47% in the ixazomib group: 49% in the placebo group). The incidence of drug withdrawal due to drug dose (25% of the ixazomib group: 20% of the placebo group) or the need for treatment-related adverse events (17% of the ixazomib group: 14% of the placebo group) were not comparable between the ixazomib group and the placebo group[15, 21, 22]. Thrombocytopenia (Grade 5) was the most common adverse reaction in patients with thrombocytopenia (Grade 5) in the placebo group, while thrombocytopenia (grade 3) was the most common in the placebo group. However, the incidence of bleeding events and platelet transfusion requirements were almost the same in the two treatment groups (19% in the ixazomib group vs 20% in the placebo group). The incidence of any grade of gastrointestinal adverse events was higher in the ixazomib group. The symptoms were nausea (29% of ixazomib group: 22% of placebo group), vomiting (23% of ixazomib group: 12% of placebo group), diarrhea (45% of ixazomib group: 39% of placebo group) and constipation (35% of ixazomib group: 26% of placebo group).In addition, 9.4% of patients in the ixazomib group had grade 3 and above gastrointestinal adverse reactions, while only 3.3% of the placebo group had gastrointestinal adverse reactions. The severity of rash was high, mainly manifested as local macular papules, which were easy to occur in the first three months of treatment. 36% of patients in the ixazomib group had rashes, 5% of them had severe rashes ≥ 3 grade, while 23% of the patients in the comparison group had all levels of rashes, and 2% of the patients had severe rashes of grade 2 or above. Three patients in the ixazomib group discontinued at least one drug for rash, and one patient in the placebo group stopped taking lenalidomide[15, 21, 23]. In addition, when ixazomib was used in combination with pomadomide and dexamethasone[24]74% (n = 23) of multiple myeloma patients had grade 3 or above adverse events. The most common adverse events were neutropenia, thrombocytopenia, anemia and infection. Two patients needed to stop treatment due to treatment-related grade 3 pulmonary infection and grade 4 febrile neutropenia. This requires us to be alert to the adverse reactions of ixazomib. When there are adverse reactions, the dosage should be adjusted as soon as possible to avoid the potential long-term complications and the risk of drug withdrawal[25]. Phase III clinical trials showed that 74% and 69% of patients in the ixazomib group and

placebo group had at least grade 3 adverse events. Higher grade thrombocytopenia, any grade of rash and low grade gastrointestinal adverse reactions were more common in the ixazomib group. The thrombocytopenia rate was 31% in the ixazomib group and 16% in the placebo group. The incidence of peripheral neuropathy was 27% (2% of grade 3) in the ixazomib group and 22% (2% of grade 3) in the placebo group[26].

A small phase 2 clinical trial is underway[27]. Objective to evaluate the effect of ixazomib on bone remodeling in patients with relapsed and refractory multiple myeloma by imaging and measuring the osteoblast activation marker (nct02499081). The positive effect of ixazomib on bone remodeling was observed in preclinical studies. In addition, good tolerance, limited toxicity and convenience of oral administration of ixazomib were observed in the clinical environment, suggesting that the drug may provide a feasible treatment option for patients with multiple myeloma with severe bone disease and pain.

5. Summary

At present, ixazomib combined with lenalidomide and dexamethasone has become one of the standard methods for the treatment of relapsed and refractory multiple myeloma[28]. Ixazomib is not only suitable for relapsed and refractory patients, but also active and effective for maintenance treatment of patients with complete remission and high cytogenetic risk of multiple myeloma. Because the route of administration is oral administration, it greatly improves the medication compliance of patients.Compared with carfilzomib,the incidence of cardiovascular and renal adverse events was lower. As mentioned above, in a large phase III trial involving 722 patients[18]. In addition to lenalidomide and dexamethasone, the adverse events did not increase. In the major subgroups, including patients who had received bortezomib or lenalidomide, and patients with high-risk cytogenetics, the efficacy of ixazomib remained unchanged[23].

To sum up, for the newly diagnosed and newly treated patients, the efficacy of ixazomib is beyond doubt, which can well alleviate the depth of myeloma cell infiltration. For elderly patients, frail patients and patients with poor treatment compliance, ixazomib is more simpler and convenienter. In patients who have obtained CR, ixazomib for maintenance treatment also has good curative effect.It is still necessary to evaluate the efficacy and safety of ixazomib in large-scale population, which needs more high-quality randomized controlled trials and long-term follow-up to help us further understand the efficacy and safety of ixazomib in patients with multiple myeloma with different characteristics and different regimens.

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