Review Article

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Current approaches and advance in mantle cell lymphoma treatment

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Abstract: Mantle cell lymphoma (MCL) is a set of heterogeneous non-Hodgkin lymphoma characterized by involvement of lymph nodes, spleen, bone marrow and blood. Under conventional treatment, survival time is 4 to 5 years with short remission period and there is still no standard treatment for MCL. In general, a close observation period called "watchful waiting" is used in elderly patients with low-risk slow clinical progress. And intensive chemotherapy including high-dose of cytarabine ± autologous hematopoietic stem cell transplantation (auto-HSCT) is recommended for younger and fit patients. Allogenic stem cell transplantation (allo-SCT) and drugs targeting the cell metabolic pathway, such as bortezomib (NF-κB inhibitor) and lenalidomide (anti-angiogenesis drug), are considerable treatments for relapsed/refractory patients. Clinical trials and less intensive chemotherapy such as R-CHOP (rituximab with cyclophosphamide, hydroxydaunomycin, oncovin and prednisone) and R-bendamustine should be considered for elderly MCL patients who are at intermediate/high risk. Recent clinical trials with ibrutinib (Bruton's Tyrosine Kinase inhibitor) and temsirolimus (mTOR inhibitor) have shown excellent efficacies in the treatment of MCL. This review will introduce the present status and major therapeutic progress in the treatment of MCL over recent years in order to provide a cutting edge to look into promising clinical progress of MCL.

Keywords: Mantle cell lymphoma (MCL); standard chemotherapy; advance

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Introduction

Mantle cell lymphoma (MCL) is a rare subtype of B cells non-Hodgkin's lymphoma (NHL), comprising about 6% of all NHL cases. MCL is associated with a characteristic chromosomal translocation t(11;14)(q13;q32) which moves the BCL-1 locus to the gene enhancer region of immunoglobulin heavy chain, causing overexpression of cell cycle regulator cyclin D1, resulting in a disorder of regulation in cell proliferation (1). MCL mainly affects elderly patients (median ages are 60 to 70 years old) with male predominance (M=75-80%). Most patients present systemic illness and at advanced stage III/IV accompanied by extranodal involvement, which is commonly present in MCL, especially in bone marrow (>65%) and gastrointestinal tract when diagnosed.

MCL is a highly heterogeneous disease, which, like indolent lymphoma, shows resistance to most common chemotherapy drugs, but also presents the same invasive characteristics as aggressive NHL. Currently, allo-SCT with high treatment-related mortality (TRM) may be the only curative treatment for MCL. MCL is characterized by high relapse rate and high response to initial treatment which leads to intensive chemotherapy that is beneficial to

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younger patients but should not be recommended for elder ones according to the overall prognosis. It is a challenge for clinical doctors in hematological tumor treatments. Nowadays, new chemotherapy drugs are constantly emerging and clinical trials are underway to study the corresponding new treatments. Molecular targeting drugs, such as temsirolimus and imbruvica have already been approved for application in clinical treatment and achieved satisfactory curative effects. This review will address two aspects of MCL treatments. The first part is about the current treatments of MCL, including conventional drugs and standard treatments such as hematopoietic stem cell transplantation (HSCT); the second part is introduction of progress in MCL treatment with new drugs undergoing clinical trials.

Current standard treatment in MCL

Treatment of MCL has made great progress since targeted therapy became a front-line treatment for lymphoma in the last decade. Intensive induction regimen followed by high-dose chemotherapy and auto-HSCT should be recommended for younger patients and less intensive combination chemotherapy a more appropriate option for elderly patients.

Front-line treatments for young patients in good physical condition

MCL is an aggressive lymphoma, of which spell acronym CHOP is a standard regimen for newly diagnosed patients. Gibson *et al.* summarized various MCL treatment options, of which total efficacy rate of CHOP is about 75%, complete response rate (CRR) 20-70%, the median progression-free survival (PFS) 10-16 months and median survival duration 3 years (2). Most therapeutic strategies adopted CHOP as an initial standard treatment for MCL due to its less toxicity and good tolerance. Although the CHOP shows high response rate, the average response duration is only 1.5 years followed by inevitable relapse among most patients after being treated by intensive induction or high-dose chemotherapy plus auto-HSCT.

Rituximab, as a highly specific mouse/human chimeric antibody to CD20, is able to improve the treatment efficacy of MCL. Research shows that overall response rates (ORR) of R-CHOP for initial diagnosed patients is 96%, CRR 48% and median PFS 16 months. However, subgroup analysis indicates that the PFS of the patients in molecular remission is similar to the ones in non-molecular remission (18.8 *vs.* 16.5 months) (3). A 65-month medium follow-up randomized research conducted by the German Low Grade Lymphoma Study Group (GLSG) reveals that (4), compared to CHOP, RCHOP showed more significant ORR (94% *vs.*75%), CRR (34% *vs.* 7%), duration of response (29 *vs.* 18 months) and time to failure (TTF) (median 28 *vs.* 14 months). However, the overall survival (OS) for CHOP and RCHOP did not show significant difference (5-year OS is 59% *vs.* 46%).

Induction therapy combined with high dose of Cytarabine showed longer PFS (60-90% of 3-year), which indicates that Cytarabine plays an important role in the induction therapy, and high-intensity R-HyperCVAD/MA treatment is usually better for MCL patients in good physical condition (5). A stage II clinical trial studied 97 patients with ECOG scores of 0 and 1, and found the objective response rate of 97% (CR/CRu rate is 87%) by R-HyperCVAD/MA treatment (6). After 10 years of follow-up, a study showed that the median TTF is 4.6-year but the median OS has not yet been reached. The patients aged ≤65 years showed higher TTF and OS of 8 years (46% and 68%) compared with the older patients (16%, P=0.003; and 33%, P=0.0007). Therefore, for the younger MCL patients in good physical condition, R-HyperCVAD combined with high-dose of cytarabine is an excellent option in initial treatment, as well as R-CHOP, also can be a good option in treatment.

Treatment for elderly patients

According to the data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, the median age of onset for MCL is 68 years old and increases yearly, which has made the treatment for elderly patients with MCL become a growing problem demanding a prompt solution (7). Because of aging-caused decreased drug tolerance and increased complications, the treatment options for older MCL patients are fewer than that for younger patients. Considering the treatment-related complications, a period of close observation should be recommended to elderly patients with low-risk at phase I/II. Single-center study showed that delayed treatment does not affect the OS of patients, especially for those asymptomatic elderly patients with low tumor burden and low Ki67 (8). The European MCL Working Group studied 560 patients aged over 60 years (median age is 70 years) who were treated by 8 cycles of R-CHOP or 6 cycles of

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R-FC. The results showed the median OS for R-FC better than R-CHOP (40 *vs.* 64 months , P=0.0072) with similar toxicity, which suggests that R-FC is a better treatment option for elderly patients with MCL (9). Patients who responded to the initial treatment were then randomly assigned to Rituximab or INF-α maintenance group for maintenance therapy. The 4-year remission in Rituximab maintenance group is 57%, twice as high as that in the latter. The result showed that the rituximab maintenance therapy has further improved the efficacy for patients who responded to the CHOP/FC treatment.

Bendamustine is a new member of the family of Alkylating agent whose efficacy in treatment for relapsed MCL patients is confirmed by studies when combined with rituximab. In a randomized controlled study including 93 patients older than 70 years with NHL (including MCL), the Indolent Lymphoma Working Group (STiL) compared combination treatment of bendamustine plus rituximab (BR) with R-CHOP and revealed that BR significantly prolonged PFS with less toxicity *vs.* R-CHOP (10). A preliminary report from BRIGHT study also showed that BR is equivalent to RCVP or RCHOP in CR rate (11). Based on the result above, BR treatment has become an ideal option for elderly patients with MCL, especially for those to whom doxorubicin cardiotoxicity is a concern. In the United States, the clinical studies on BR and other induction treatment are ongoing (ID: E1411, S1106). Bortezomib is added to the induction treatment and rituximab ± lenalidomide are selected in maintenance therapy for the patients at 60 years and older, the research result of which is worthy of expectation.

Treatment strategies for relapsed/refractory patients

Currently, there is no completely effective treatment available for relapsed/refractory patients with MCL, except the allogeneic hematopoietic stem cell transplantation (allo-HSCT). Therefore, the goal of treatment for those patients is long-term control of disease through building a balance between efficacy and toxicity to improve life quality.

Chemotherapy-based treatments

Treatments including combined R-CHOP procedure increase the treatment response rate to 60-70% in patients with MCL. However, the duration of response for relapsed/refractory patients remains limited (mostly less than 1 year). Therefore, the R-CHOP and other treatments are considered as palliative treatments. Conversely, rituximab combined with other drugs has achieved better results, such as with bendamustine relapsed/refractory patients showing 75% of ORR and 50% of CRR. A clinical study on rituximab plus cytarabine combination treatment for 20 relapsed patients and 20 initial patients with MCL showed prominent efficacy (12). The ORR of relapsed patients is 80%, CRR is 70% (all patients ORR is 90%, CRR is 83%), 2-year PFS reaches 70% of which 95% are the patients who had been subjected to initial treatment and their main toxicity was reversible myelosuppression.

Coleman *et al.* (13) proposed a unique palliative treatment program for relapsed elderly patients by taking orally low-dose "metronomic" chemotherapy such as oral prednisone, cyclophosphamide, etoposide, procarbazine and hydrochloride, which showed efficacy in 82% of patients from 22 MCL cases. This low-dose "metronomic" oral chemotherapy treatment with multiple chemotherapy drugs for MCL is well tolerated and able to be combined with Rituximab and Thalidomide which is worthy of further investigation in a larger samples.

Proteasome inhibitor

Bortezomib is the first approved chemotherapy drug by U.S. Food and Drug Administration (FDA) for the treatment of relapsed MCL [2006]. It regulates various cellular processes, including signal transduction and apoptosis initiation through selective and reversible inhibition proteasome 26s activity. Targeting the over expressed NF-κB pathway by bortezomib in MCL has become the focus of studies. A multi-center phase II clinical trial held by PINNACLE confirmed the efficacy of Bortezomib alone in treatment for 155 relapsed patients with MCL (14) in which ORR is 33% (CR/CRu is 8%), median OS about 2 years and the median TTP 6.7 months. For patients who responded to initial treatment showed that the median TTP is 12.4 months and median OS is 35.4 months. Some clinical center has adopted Bortezomib combination as the front-line treatment for relapsed/refractory patients with MCL, such as BR + bortezomib, R-CHOP + bortezomib, R-HyperCVAD + bortezomib, other biologics + bortezomib, etc. Ruan *et al.* studied R-CHOP + bortezomib combination treatment for 20 patients with MCL at stage II clinical trial and showed its efficacy more than 95%, including CRR of 80% with primary side effect neurotoxicity (level 3 neurotoxicity incidence is 5%) (15). An ongoing phase III clinical trial is also expected, in which the treatments of Bortezomib plus R-HAD or R-HAD alone are conducted in relapsed patients randomly (ID No: NCT01449344). Diverse new

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proteasome inhibitors including some in oral administration form are being evaluated in clinical studies.

Immunomodulatory drugs

Thalidomide showed its therapeutic effect on MCL a decade ago. Recently in France, its efficacy on relapsed MCL has been confirmed in a retrospective study involved 58 patients through showing the ORR of 50% (with an additional 29% stabilized condition), with a 1- and 2-year TTF of 29% and 11%, with acceptable side effects (3-4 level adverse reactions accounted for 7%) (16). Therefore, thalidomide is a highly cost-effective option with good tolerance compared to more expensive targeting drugs, especially for the countries with poor medical conditions. Lenalidomide, as a thalidomide analogue, has been confirmed for its response rate and anti-lymphoma effect in relapsed MCL patients by some phase II clinical trials, showing the ORR of 30-50%, CRR of 20% and PFS of 6-9 months. A recent phase II clinical trial for 52 patients with relapsed MCL has confirmed the comparatively high response rate of lenalidomide + rituximab combination (57% of ORR and 36% of CRR) with response duration up to 19 months (17). Moreover, with manageable toxicity (low hematological toxicity) and convenience, oral drug formula has conferred Lenalidomide a promising prospect in maintenance treatment, especially for elderly patients. Currently, a phase II clinical trial studying the combination treatment of rituximab-lenalidomide-bendamustine in relapsed MCL patient is enrolling (ID: NCT01737177).

Hematopoietic stem cell transplantation

Autologous hematopoietic stem cell transplantation (auto-HSCT)

Like the treatment of diffuse large B-cell lymphoma, auto-HSCT initially was applied to MCL patients to whom the previous therapy was unable to achieve CR and to lately relapsed MCL patients. The first study involved 40 MCL patients, most of whom did not reach CR before they received auto-HSCT showing 35% of 2-year EFS and 65% of 2-year OS. For those patients, receiving three therapies prior to the auto-HSCT was an important negative factor affecting the outcome of transplant (18). Fenske evaluated efficacy of auto-HSCT in 151 relapsed MCL patients and revealed the cumulative progression rate of 50% and OS of 40% by 5 years following transplantation (19). Since the traditional transplantation treatment was not effective for relapsed MCL patients, researchers had constantly explored new drugs and treatment combinations, which achieved progressive results. Gopal reported that 16 cases of relapsed MCL patients who received ^{131}I-Tositumomab combined with high-dose of Cyclophosphamide and Etoposide showed 93% of OS and 61% of PFS by 3 years following transplantation (20). This treatment might be a good option for relapsed MCL patients after taking auto-HSCT since MCL is sensitive to radiotherapy.

Auto-HSCT has been studied more often as a consolidation therapy for MCL patients under initial remission due to its inferior effect on relapsed patients.

The federation of European MCL conducted a randomized trail dividing MCL patients who are taking standard dose induction into interferon maintenance group and high-dose of Cyclophosphamide combined with TBI following auto-HSCT group, then the PFS of auto-HSCT group was significantly superior to interferon maintenance group (39 *vs.* 17 months, P=0.01) (21). Another important finding of this study is that the induction treatment including rituximab could increase PFS (48 months), however, the 3-year OS between the two groups had no significant difference (83% *vs.* 77%, P=0.18) showing a lack in plateau in the survival curve which indicates that relapse occurred eventually in many patients. Therefore, researchers continue to improve induction and transplantation procedure in order to increase efficacy of treatment. Dreger *et al.* significantly improved the 4-year EFS (83% *vs.* 47%, P=0.04) with extended plateau on EFS curve by adding rituximab to the cyclophosphamide plus TBI in combination (22). Nordic Lymphoma Working Group adopted rituximab plus HyperCVAD/MA induction treatment followed by auto-HSCT consolidation after *in vivo* purging with Rituximab in MCL patients. The group reported the ORR of 96%, CRR of 54%, 6-year OS of 70%, EFS of 56%, and PFS of 66%, with no relapsed patients after a 7.5-year follow-up (23). MDACC retrospectively analyzed the data of 17 years and concluded that R-HyperCVAD treatment significantly improves the efficacy in the treatment of MCL that is approved by 90% of CRR and 60% of PFS when utilizing R-HyperCVAD as the front-line treatment for young patients with MCL. 50 MCL patients under remission induced by R-HyperCVAD showed PFS and OS of 6 years as 39% and 61% after taking auto-HSCT (24). A publication from Nebraska Medical Center revealed that the 4-year OS in 58 patients who received above treatment is 78%, compared to 47% in patients without transplantation (P=0.03) (25). Researchers have been trying to reduce the toxicity of the Hyper-CVAD

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treatment which has usually been recommended for patients under 60-65 years old because of its strong toxicity to the hematopoietic system, with a transplant-related mortality of 2-5%. Kahl *et al.* reported 77% of ORR and 64% of CRR by removing large doses of Methotrexate and Cytarabine, while adding Rituximab for maintenance (26). The cancer and leukemia group B (CALGB) achieved a 67% of response rate by removing the high-dose methotrexate and keeping cytarabine which shows similar result to the SWOG study concerning methotrexate and cytarabine, suggesting that high-dose of cytarabine is critical for prompt efficacy of treatment against MCL (27).

In conclusion, high-dose chemotherapy plus auto-HSCT is a good option in front-line consolidation treatment for young MCL patients who obtained complete remission after induction. However, relapse is still the biggest challenge following auto-HSCT. Most patients still would show late relapse after taking sequential high-dose chemotherapy including strongest R-hyperCVAD and auto-HSCT in 5 years. Therefore, the significant challenge for scientists is to explore new solutions to this problem, such as adopting more effective induction drugs, optimizing transplantation and appropriate maintenance therapy after transplantation.

Allogeneic hematopoietic stem cell transplantation (allo-HSCT)

Although auto-HSCT can be used for some particular patients to prolong PFS, it is still unable to cure the disease. Allo-HSCT may help patients to achieve long-term survival and even cure them because of its graft-versus-lymphoma (GVL) effect. Nevertheless, high non-relapse mortality (NRM) after myeloablative transplantation limited its clinical application and promotion. Intensity-reduced pretreatment (RI) allo-HSCT lowered the risk of transplantation in early stage and could be applied to a wider range of patients. A prospective study in the UK enrolled 70 relapsed/refractory MCL patients who received RI-allo-HSCT (30-67 years old, median age is 48 years), of which 57 patients took pre-treatment including Alemtuzumab, of them 34% had received auto-HSCT previously (28). This study showed a NRM rate of 18% for 1 year and 21% for 5 years. Incidence rate of grade III/IV for acute graft versus host disease (aGVHD) is 10% and the rate of chronic graft versus host disease (cGVHD) in 5 years is 61%. Otherwise, the cumulative risk of recurrence of 5-year is 65% with 37% of 5-year OS and 14% of 5-year PFS. Due to the age and whether, they received less than two chemotherapies which are the main factors that affect OS, however, only the latter affects PFS of patients. Moreover, using alemtuzumab increased 3-year OS (28). Recently the International Blood and Marrow Transplant Database (IBMT) announced results of multiple centers study for 202 refractory patients with MCL from 1998 to 2010, of whom 74 patients accepted myeloablative allo-HSCT (median age is 54 years) and the other 128 accepted RI-allo-HSCT (median age is 59 years). The results showed that 3-year recurrence rate is 33% in myeloablative allo-HSCT group with 20% of PFS and 25% of OS, compared with 32% of recurrence rate in RI-allo-HSCT group with 25% of PFS and 30% of OS, which suggests that there is no statistical difference in NRM of 47% and 43%. The study indicated that 25% of patients with refractory MCL could get long-term relief after taking allo-HSCT and intensity of pre-treatment has no effect on transplantation efficacy (29). Another result from the same study group provided donor lymphocyte injection to 15 relapsed MCL patients after taking allo-HSCT, 11 of whom obtained CR again. The MCL study, there still requires more treatment experience accumulated. The research hotspot in this area is how to reduce the incidence of GVHD while remaining efficacy of GVL.

Treatment progress

Conventional treatments for MCL have been mostly ineffective and there are no standard treatment options. In recent years, the investigation of novel drugs based on molecular biology has achieved important progress. Most novel targeting chemotherapies in ongoing phase I or II clinical trials are based on the molecular targeting of cell proliferation and apoptosis pathways. In addition, more new cancer gene targets are being constantly discovered by molecular genetic research and have provided new preclinical evidence for drug development and clinical treatments.

B cell receptor signal blockers

Bruton's tyrosine kinase (BKT) inhibitor plays an anti-tumor role by specifically blocking B cell receptor signaling pathways for survival. An international phase II clinical trial studying the effect of BTK inhibitor ibrutinib for 51 relapsed/refractory patients showed that single drug Ibrutinib produced encouraging results with 68% of ORR and 22% of CRR in 110 evaluable patients (with or without

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previous administration of bortezomib). The long-term 15-month follow-up study demonstrated that the prolonged treatment could increase CR rate with 75% of ORR, 39% of CRR and PFS of 14 months, otherwise, reaction median time has not yet obtained by then. The safety of Ibrutinib is significant since less than 15% of patients receiving intensive treatment showed grade III/IV hematologic toxicity, mild gastrointestinal symptoms, fatigue and infection (30). Considering its superior efficacy and safety, U.S. FDA approved Ibrutinib for the treatment of relapsed/refractory MCL on 11/13/2013, which is the third drug approved by FDA for the treatment of MCL following velcade [2006] and lenalidomide [2013]. In addition, the clinical study on the treatment of MCL with BTK inhibitors in combination with other drugs (such as bortezomib) has been recruiting patients. CAL-101, as a drug targeting the signal pathway of BCR, is in the phases I and II of clinical trial. However, its final effect on the duration of remission is unknown, although good ORR (62%) results were obtained (31).

Antibody-based treatment

More and more monoclonal antibody drugs, including ones targeting CD20 are under pre-clinical or clinical research, however, the data available for MCL treatment is limited. The treatment with GA101, as a humanized CD20 monoclonal antibody, showed 27% of ORR in relapsed/refractory MCL patients. Ofatumumab, a complete humanized anti-CD20 antibody, has been accessed for its efficacy when combined with bendamustine or lenalidomide in phase I/II of clinical trials, but final study results have not been confirmed. DCDS4501A, an anti-CD79a monoclonal antibody, has showed encouraging anti-tumor efficacy in 33 lymphoma patients who received intensive pre-treatment, including 4 cases of refractory/relapsed MCL in phase I clinical trial. A long-term follow-up study is still required for confirming its efficacy and safety (32).

Treatments targeting cell cycle and apoptosis

Flavopiridol directly inhibits CDK4 and CDK6, resulting in down- regulation of cyclinD1 expression. It shows significant anti-lymphoma activity when in combination with fludarabine, rituximab or bortezomib. PD0332991, another CDK4/6 inhibitor, shows same good clinical effect in MCL patients. Oral biological formulation ABT199, a specific BCL-2 BH3 mimic, shows good efficacy in the phase I clinical trial for patients with MCL. Abexinostat, a novel pan-deacetylase inhibitor, shows good clinical activity and tolerance in phase II clinical trial for refractory/relapsed MCL patients with 27% of ORR and 4-month of PFS (33).

Inhibitors of mammalian target of rapamycin (mTOR)

Temsirolimus is an intravenous mTOR inhibitor that was approved in Europe in 2009 for the treatment of relapsed/refractory patients with MCL, effectively improved median PFS (4.8 *vs.* 1.9 months) and ORR (22% *vs.* 2%) when comparing to single-agent treatment in phase III clinical study (34). The most common side effect of Temsirolimus is hematologic adverse reactions but could be well controlled by reducing dose or delaying treatment. A phase II clinical trial including 71 patients, confirmed the efficacy of Temsirolimus in combination with Rituximab with 59% of ORR, 19% of CRR and 10-month median TTP (35). An ongoing phase II clinical trial with Bendamustine and Rituximab is aim to improve the efficacy of Temsirolimus. Everolimus, as another well-tolerated oral mTOR formulation showed 20% of ORR (including 49% of stable disease) and 5.5-month median PFS in 35 relapsed MCL patients from clinical trials of multiple centers (36).

Radioimmunotherapy

Radioimmunotherapy is a novel type of treatment coupling radionuclide with monoclonal antibody, represented by ^{90}Y-Ibritumomab tiuxetan and ^{131}I-tositumomab, are two anti-CD20 radioimmunotherapy regimens being applied in current clinics. Current study has found that the treatment with radioimmunity complexes shows efficacy in patients who exhibit rituximab resistance. ^{90}Y-ibritumomab tiuxetan shows good tolerance by refractory/relapsed patients in single-agent treatment with 42% of ORR, 26% of CRR, but only 6-month median PFS (37). Research suggests that the poor efficacy of the radioimmunity complex in patients results from large tumor burden and chemotherapy resistance. ^{90}Y-Ibritumomab Tiuxetan shows good efficacy as consolidation therapy with 84-97% of ORR (CR is 45-73%) in newly diagnosed or relapsed patients who accepted removal of tumor burden by previous treatment. CHOP treatment followed by ^{131}I-Tositumomab showed 86% of ORR and 67% of CR/CRu. The researchers evaluated the efficacy of pretreatment program with ^{90}Y-Ibritumomab Tiuxetan or ^{131}I-Tositumomab combined

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with allo-HSCT (38) and indicated that ^{90}Y-Ibritumomab Tiuxetan group is well tolerated by elderly patients with 85% of 2-year OS and 68% of PFS, moreover, the ^{131}I-Tositumomab regimen showed 100% of ORR, 91% of CRR, 93% of 3-year OS and 61% of PFS. However, the effect of high ORR on OS of patients awaits further evaluation.

Prospects

MCL is a highly heterogeneous group of malignant tumors characterized with indolence and high invasiveness. Therefore, the treatment of patients with MCL, most of whom are elderly, remains a challenge for hematologists. Over the past decade, the treatment of MCL has achieved significant progress with median survival time increased from 2.7 to 4.8 years, which has been contributed by application of targeted therapies (such as Rituximab) applied in front-line treatment, high-dose chemotherapy combined with allo-HSCT for consolidation in young patients and less intensive chemotherapy treatment (such as Rituximab plus Bendamustine) for elderly patients. Furthermore, exploring new drugs brings new hope for patients with MCL. The treatment of MCL could be further improved significantly by better understanding the heterogeneity of MCL, more individualized treatment and application of novel targeting drugs combined with conventional chemotherapy treatments.

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Footnote

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