Chapter 14

TREATMENT OF RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA

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INTRODUCTION

Mantle Cell Lymphoma (MCL) is a B-cell non-Hodgkin lymphoma (NHL) which accounts for 6% of all NHL cases, has an annual incidence of 2-3/100000, shows translocation (11,14) and CD 5 positivity, and is characterized by overexpression of cyclin D1 in 95% of cases. It is distinguished from other lymphomas with a more aggressive clinical course. Cyclin D1 negative cases may be cyclin D2 and cyclin D3 positive. In recent years, the presence of SOX11 expression has been of great importance for differential diagnosis of MCL and SOX11 positivity has provided great convenience in terms of diagnosis in cyclin D1 negative cases (1).

The average age of diagnosis is 60-65. MCL is twice more common in men compared to women. Patients are often diagnosed in later stages and present with generalized lymphadenopathies, peripheral blood, bone marrow involvement, and splenomegaly. Extranodal involvement is observed in 90% of cases. Extranodal involvement regions include the gastrointestinal system, skin, and central nervous system. Some patients may present with colonic lymphomatous polyposis characterized by colon involvement. B symptoms are seen in one out of every three cases. Hematologically, patients may present with leukemic phase characterized by pancytopenia or increased leucocyte count (2).

PROGNOSIS

Mantle cell lymphoma has a varying clinical picture from indolent course to aggressive course with relapsed and refractory disease. The average time of survival is 3-7 years. There has been attempts to develop international prognostic indices to help predict the clinical course of the disease. Follicular lymphoma was defined in the International Prognostic Index (IPI), which shows the prognosis in lymphoma patients, and the importance of the Follicular Lymphoma Interna-

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relapsed/refractory MCL. In the BORID study, bortezomib was used in combination with rituximab and dexamethasone, and led to a response rate of 81%. The use of bortezomib in combination with bendamustine and rituximab led to a response rate of 71%. Another important pathway involved in the pathogenesis of MCL is mTOR. Temsirolimus, an mTOR inhibitor, yielded a response rate of 44% and has been shown to be more effective than everolimus, another mTOR inhibitor (14). Proven themselves in treatment of multiple myeloma, immune modulator agents (lenalidomide) have been shown to be effective in MCL treatment as well. The combination of rituximab and lenalidomide led to an average response rate of 58% (15).

Venetoclax targets the protein called Bcl-2. Bcl-2 is an important protein involved in regulation of apoptosis. Venetoclax blocks Bcl-2, thereby promoting cancer cell death and destruction. As a stand alone agent, venetoclax leads to a response rate of 75%, which is a significant figure. Another point to be considered in venetoclax treatment is possible tumor lysis. The combination of venetoclax and ibrutinib has a synergistic effect on apoptosis. Independent from MIPI, this combination leads to a 50% response rate in patients with 17 p deletion. Combinations of venetoclax with other agents are still studied (11, 16, 17).

The CAR-T cell treatment is a renowned immunotherapy approach which has given encouraging results in diffuse large B cell lymphoma and relapsed/refractory B cell non-Hodgkin lymphoma cases, which involve MCL as well. The ZUMA-2 study (NCT02601313), which examines the reliability and effectiveness of autologous CD-19 CAR T-cell structure in relapsed/refractory MCL cases which are non-responsive to ibrutinib, is still ongoing. Whether or not the CAR-T cell treatment will be effective in MCL cases is not known with certainty; however, it is potentially a curative approach in select cases other than the limited role of allogeneic stem cell transplantation. Allogeneic stem cell transplantation seems to be the only option offering a curative treatment. There are allogeneic transplantations applied with diluted preparation regimes.

In conclusion, MCL usually responds to chemotherapy; however, it results in quick relapse and chemotherapy-resistance. Therefore, risk factors should be examined thoroughly and the treatment should be planned specific to the patient. Studies on treatment of MCL with combinations of new agents are still ongoing.

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