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Mantle Cell Lymphoma: Effectiveness of Maintenance Ibrutinib – Case Report

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Abstract

Mantle cell lymphoma is a rare subtype of non- Hodgkin lymphoma with life-threatening course of disease. It mostly affects older adults in their sixth or seventh decade of life with

male to female predominance of 3 to 1. Its prognosis is very poor and the treatment is demanding. The golden standard therapy for younger, fit patients <65 years is chemoimmunotherapy such as R-CHOP/R-DHAP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, prednisolone, dexamethasone, cytarabine and cisplatin) followed by BEAM chemotherapy (carmustine, etoposide, cytarabine, melphalan) and autologous-stem-cell transplant (ASCT). Nevertheless MCL is mainly recognized in patients of average age 67 in whom comorbidities often play a crucial role during treatment.

A 56-year-old patient was admitted to the Department of Hematooncology and Bone Marrow Transplantation with clinical symptoms such as heavy night sweats, generalized enlargement of lymph nodes, massive weight loss, dyspnea and fatigue. Initial physical examination and imaging showed enormous hepatosplenomegaly, mass in the lungs and fluid in the pleural cavity.

The patient underwent chemoimmunotherapy consolidated with an autologous stem cell transplant. To date, the patient is on maintenance treatment with ibrutinib.

Introduction

Mantle cell lymphoma (MCL) is a relatively rare type of non-Hodgkin B-cell lymphoma with an aggressive clinical course. It affects elderly people, with the median age of diagnosis from 60 to 70 years old. MCL combines characteristics of both indolent and aggressive lymphomas and it is largely incurable with conventional chemoimmunotherapy. Intensive combined therapy is commonly consolidated with an autologous stem cell transplant (ASCT) [1]. MCL consists of cells with irregular nuclei and it infiltrates the mantle zone surrounding the germinal centers. The key event of molecular pathogenesis (95% of cases) is the gene translocation (t(11;14)(q13:32), hence the overexpression of CCND1 (cyclin D1). Its continuous production results in the disturbance of cell cycle in G1-S phase. The typical antigens expressed by MCL B-Cells are CD19, CD20 and CD5. Treatment of mantle cell lymphoma patients is a challenge and the median survival rates are poor – 3 to 5 years [2]. However, Bruton tyrosine kinase inhibitor ibrutinib is a very promising agent for patients with MCL [3].

Case Report

56 -years-old man was admitted to the Department of Hematooncology and Bone Marrow Transplantation with clinical symptoms such as heavy night sweats, generalized enlargement of lymph nodes, massive weight loss, dyspnea and fatigue. Imaging studies showed massive lymphadenopathy in both the thoracic and abdominal cavities, hepatosplenomegaly and pleural effusion. Surgical lymph node biopsy was performed and the histopathology results showed dense monoclonal lymphocytic infiltration of CD20, CD19 and CD5 antigens (Fig. 1). The immunotyping of cancer cells showed the presence of cyclin D1 and high proliferative

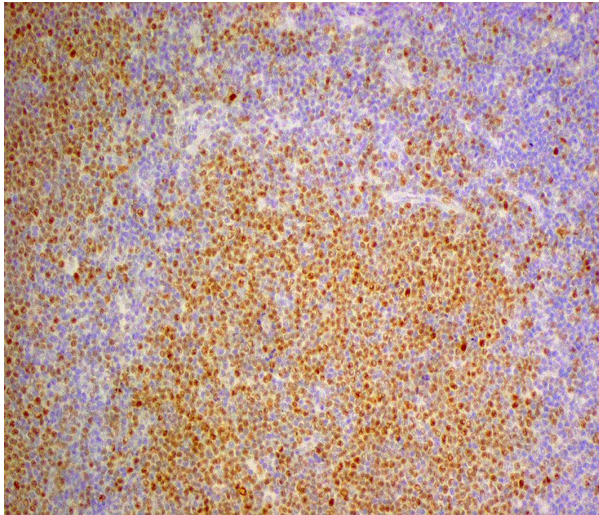
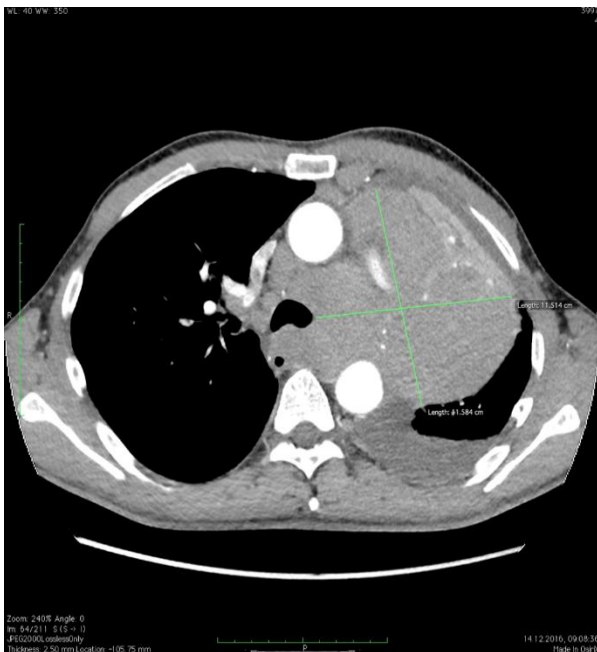


Fig. 1. Immunotyping of biopsy shows expression of Cyclin D1

index Ki67 = 70%. MCL patients typically have stage III or IV disease at the time of diagnosis, with extensive lymphadenopathy, splenomegaly, blood and bone marrow involvement. After further examination, which included a CT scan of thorax and abdomen the patient was diagnosed with MCL stage IV. Computer tomography of the thorax showed an extensive enlargement of mediastinum with dimensions of 11,514 cm x 11,584 cm caused by



lymph nodes and hydrothorax (Fig. 2) The CT scan of abdomen displayed hepatosplenomegaly with spleen index of 2220 cm³ (Fig. 3).

Fig. 2. Computer tomography scan of the thorax.

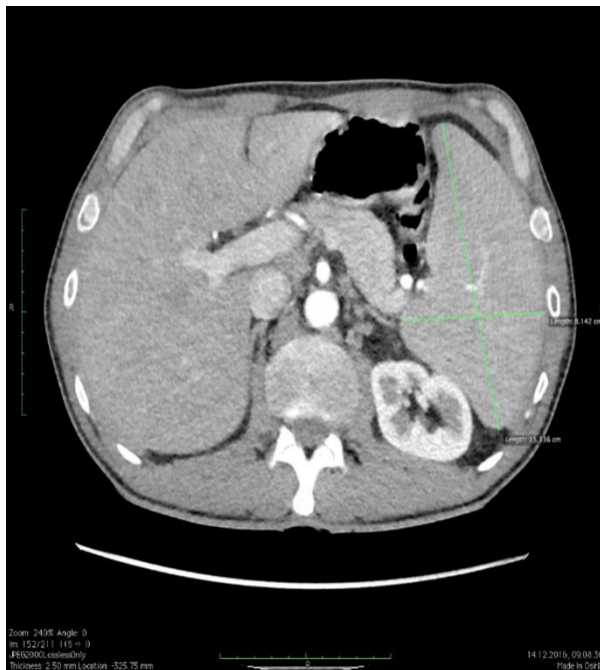


Fig. 3. Computer tomography scan of the abdomen.

Therapeutic regimens include multiple chemotherapy drug administrations in combination with rituximab. Rituximab is a chimeric monoclonal antibody against the CD20 of lymphocyte B. The patient was qualified for chemoimmunotherapy by turns R-CHOP and R-DHAP. The treatment was introduced every 4 weeks. During treatment, the patient developed toxicities (thrombocytopenia, anemia, granulocytopenia), requiring substitution treatment (RBC, RBC, granulocyte growth factor). After completion of the entire planned course of chemotherapy, after clinical reassessment, complete remission (CR) of the underlying disease was noted. The patient was qualified for autologous stem cell transplantation (ASCT). The conditioning protocol used BEAM in full doses. 6.0×10^6 / kg CD34 + cells were administered, with good tolerance. During the entire post-transplant period, no life-threatening complications were observed. The patient was discharged home in good general condition. The control PET examination performed after 2 months did not reveal the presence of active neoplastic disease and confirmed the maintenance of complete remission. Ibrutinib at a dose of 540 mg / day was used as a maintenance treatment. Up to the time of this study, no side effects were observed throughout the observation period, while CR was maintained.

The patient is already 4 years in complete remission and constantly on maintenance treatment with ibrutinib.

Discussion

Mantle cell lymphoma belongs to the group of lymphomas with an aggressive clinical course, the treatment of which is often successful in response to induction chemoimmunotherapy, but usually of a very variable duration. A significant fact is the high risk of disease recurrence

after variously long remission periods. It may occur even several years after induction treatment and consolidation[4,5,6].

To improve these still unsatisfactory effects of treatment, the possibility of using maintenance treatment is being considered. It is usually defined as a low-intensity therapy that can be used safely over a long period of time in a patient who has responded to induction therapy. Its intention is not to cure (usually impossible to achieve), but to maximize the duration of disease complete remission with a chance of prolonging overall survival (OS) [7].

Maintenance treatment is usually recommended in the group of incurable, using standard chemoimmunotherapy regimens of hematopoietic diseases (multiple myeloma, indolent lymphomas). It targets cancer cells that survived the induction treatment and are in a specific "dormant" state. A very important element of maintenance treatment is the selection of an appropriate drug, which on the one hand should be effective as well as well tolerated, with as little toxicity as possible and not requiring frequent outpatient or hospital visits. This is important assuming the need for long-term use. At present, we do not have much data from randomized clinical trials on the maintenance treatment of MCL patients. One of the first was a study conducted by the European Organization for the Research and Treatment of Cancer Lymphoma Cooperative Group, which assessed the effectiveness of interferon- α 2a maintenance treatment for one year in 25 patients with MCL. There was statistically insignificant longer PFS and overall survival [8].

The maintenance treatment with rituximab was the subject of most studies. The Swiss Group for Clinical Cancer Research (SAKK) study included both newly diagnosed (37%) and previously treated (63%) patients with MCL. Following induction treatment, the entire group was randomized to two subgroups: with and without maintenance treatment. However, no statistically significant differences were found in event-free survival (EFS) [9].

In a group of 47 patients with MCL, analyzed by the German Low Grade Lymphoma Study Group (GLSG) receiving R-FCM induction chemotherapy and then randomized to rituximab maintenance or follow-up, no significantly longer duration of response or OS was observed [10].

An important problem is to answer the question, whether repeated application of a drug, in this case rituximab, as part of induction treatment, may be an effective strategy aimed at eradicating cells that have already managed to "escape" from its effects once. It has been suggested that the tumor cells may lose the target antigen, locate it in places difficult to access for monoclonal antibodies, NK cells and macrophages. However, as long as the exact mechanisms of drug resistance and the factors leading to the transition from remission to exacerbation are unknown, the choice of maintenance therapy is often empirical [7].

Despite the previously unsatisfactory effects of rituximab in maintenance therapy, later reports were more optimistic. They came from the studies of Kluin-Nelemans et al. The authors indicated a statistically significantly longer duration of remission and OS in the group of older (60-65 years) patients with MCL who received R-CHOP chemotherapy in induction treatment and rituximab in maintenance treatment, compared to patients given INF- α .

However, this relationship was not confirmed in patients receiving induction with the R-FC regimen [11].

The results of the LYMA study also turned out to be very interesting. They included younger, untreated MCL patients (18-65 years old). In the induction treatment, the R-DHAP system was administered (in the absence of a satisfactory response, additionally R-CHOP-14), followed by autotransplantation of bone marrow stem cells, after conditioning treatment with R-BEAM. After randomization, patients received rituximab maintenance treatment or were only under clinical observation. A statistically significantly longer EFS was demonstrated and, which was particularly important, a longer OS. [4] This study was one of the group dedicated to autotransplanted MCL patients. Other retrospective studies also suggested the potential benefits of chronic rituximab use in the post-transplant period [12, 13, 14]. There are also attempts to use other anti-CD20 monoclonal antibodies in maintenance therapy: ofatumumab and obinutuzumab, supported by quite promising results of preclinical studies [15, 16]. Currently, only single reports are known about the possibility of their administration in patients with relapsed / refractory MCL [17, 18].

Mondello et al. used ibritumomab tiuxetan as a consolidation treatment after chemoimmunotherapy and autologous hematopoietic cell transplantation, followed by a two-year infusion of rituximab. As demonstrated by the authors, this allowed for a significant extension of progression-free time and overall survival [19].

An interesting proposal was also an attempt to use bortezomib as a consolidation or maintenance treatment in patients after ASCT who had previously received two doses of rituximab (CALB 50403 study). The final results of the studies suggested progression-free survival benefits of bortezomib maintenance therapy. However, threats resulting from the neurotoxicity of bortezomib, especially in long-term use, have also been pointed out [20]. Therefore, attention was paid to higher-generation proteasome inhibitors with less potential for side effects: carfilzomib (study NCT01926665) and ixazomib (study NCT02632396).

The patient described by us was receiving ibrutinib for maintenance treatment. The molecule of Bruton's kinase was a breakthrough in the treatment of hematopoietic system diseases, including MCL. Permanent stimulation of the B cell receptor is considered to be the major pathogenetic factor in the development of MCL and therefore blocking the signaling pathway from this receptor clearly justifies the use of ibrutinib. Already as an independent drug, it shows significant activity, which was confirmed by both phase 2 and 3 studies [21,22]. They mainly concerned the resistant or relapsed form of MCL, which was a particularly difficult therapeutic problem. The immunomodulatory effect of ibrutinib on the microenvironment was the basis for trials of its combination with lenalidomide. Jerkeman et al. Have published promising results of treatment of this very unfavorable group of patients with the above-mentioned drug system, to which rituximab was also added. The role of lenalidomide in this regimen was i.a. counteracting the antagonism between ibrutinib and rituximab suggested by some researchers (inhibiting the direct and indirect effect of ibrutinib on NK cells) [23, 24]. In the preliminary analysis, the authors indicate a possible beneficial effect of the combined use of ibrutinib, lenalidomide and rituximab, which requires confirmation in further studies [25].

At present, we do not have results of randomized trials that could reliably confirm or negate the efficacy of ibrutinib maintenance therapy in patients with MCL. We are waiting for the results of the SHINE study (BR / rituximab vs BR + ibrutinib / rituximab + ibrutinib in maintenance) and the European TRIANGLE (CHOP, R-DHAP, ASCT vs CHOP, R-DHAP, ASCT / ibrutinib vs CHOP, R-DHAP / ibrutinib in holding).

The importance of lenalidomide in the maintenance treatment of autologous stem cell transplantation was assessed in study NCT02354313. 300 MCL patients were randomized, one group receiving lenalidomide 10-15mg / day on days 1-21 for 28-day cycles for 2 years after induction treatment, while the other group was only under clinical follow-up. The problem of long-term use of lenalidomide is its considerable toxicity (cytopenia, increased risk of thrombosis) and the possible possibility of secondary neoplasms (observed in patients with multiple myeloma) [26].

Conclusion

Mantle cell lymphoma is a difficult therapeutic problem. This applies to both the possibility of obtaining a response to treatment as well as the further management strategy: the need for maintenance treatment, the selection of an appropriate drug and an effective and safe dose. Ibrutinib may be one of the possible forms of this type of therapy to be considered (good tolerance, convenient dosage). Although an improvement in the outcomes of MCL patients is recently observed, the future is to improve the long-term outcomes of therapy, especially among younger patients.

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