CD30 – The head of TNF-family… or a successful story of brentuximab vedotin

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SUMMARY

Hodgkin lymphoma and anaplastic large cell lymphoma are malignancies that highly express CD30 antigen on the cell surface. Both are generally curable by standard chemotherapy but refractory diseases and relapses are treatment problems. Brentuximab-vedotin is a labeled monoclonal antibody against CD30 and it is approved for the treatment of Hodgkin lymphoma relapsed after autologous stem cell transplantation and for relapsed anaplastic large cell lymphoma. This is the first drug approved for the treatment of Hodgkin lymphoma after 30 years.

Key words: *Hodgkin Disease; Antigens, CD30; Antineoplastic Agents; Antibodies, Monoclonal; Lymphoma, Large Cell, Anaplastic; Hematopoietic Stem Cell Transplantation*

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INTRODUCTION

Hodgkin lymphoma (HL) is a relatively rare malignant disease, originating from B-lymphocytes, which represents 0.6% of all malignant diseases worldwide. It is significant because it mostly occurs in young people. Median age of the patients is 38 years, and in 40% of cases it occurs in patients younger than 35 (1). A standard first line therapy which includes chemotherapeutic protocols ABVD (doxorubicin, bleomycin, vincristine and dacarbazine) or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone and procarbazine), with or without radiation therapy, cures 60-90% of the patients, depending on the stage of the disease. Between 5-10% of patients is initially refractory to the first line treatment, while 20-30% of the patients experience relapse, after the initial response to therapy. Standard treatment in relapse/refractory disease is high-dose chemotherapy with autologous hematopoietic stem cell transplantation (ASCT), which approximately cures another 50% of patients (2). Median time to progression with the next therapy, in patients who experience relapse after the transplantation, is 3.8 months, and a median survival is 26 months (3).

Anaplastic T-cell lymphoma (ALCL) belongs to the group of mature T-cell lymphomas and is characterized by expression of CD30 receptors at the cell surface. In 65-80% of cases, the ALK (anaplastic lymphoma kinase) protein is excessively expressed. This protein expression determination is of a key importance for the disease prognosis. A five-year survival of ALK + ALCL is from 71-93%, while the survival of ALK cases is about 40% (4, 5). The standard first line therapy for ALCL is not completely defined. In ALK+ cases, the CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy, with or without etoposide, leads to long-time survival in most of the patients. On the other hand, in ALK-, the CHOP achieves moderate results, so the autologous transplantation is the standard of treatment in the first line, and with such intensive approach, a five-year survival without the disease progression is 64%, which is longer than in other peripheral T-cell lymphomas (6).

CD30

CD30 is a transmembrane protein which belongs to a large family of tumor necrosis factor (TNF) proteins. Cytoplasmatic part of this protein contains the TRAF (TNF-receptor associated factor), which modifies activation of the nuclear factor kappa B (NF-κB). An excessive expression of CD30 leads to constant activation of NF-κB, independent from the existence of ligands for CD30, which leads to blockage of apoptosis and the unlimited survival of cells. Physiological role of CD30 molecule has not been defined yet. It is considered to participate in the immune response, but it is expressed in a small number of B- and T- lymphocytes, while its expression is somewhat greater with the presence of interleukin 4, during T-lymphocytes activation (2). On the other hand, in the Reed-Sternberg cells of Hodgkin lymphoma, as well as in the ALCL cells, CD30 protein expression is extremely high. This makes it an attractive target for the target therapy, because it is very selectively expressed in malignant cells (7). Besides this, a high level of the soluble CD30 is in correlation with worse prognosis in patients with HL (8).

Unconjugated anti-CD30 antibodies

After recognition of the CD30 receptors as an interesting target in the CD30-positive malignancies' therapy, two monoclonal antibodies, which blocked this antigen were developed: chimeric SGN-30 and human MDX-060 (9,10). SGN-30 was tested in HL and ALCL in phase II trials. Although there was no severe toxicity, there was also no response to treatment in patients with HL, while in patients with ALCL, the overall response rate (ORR) was 17%, and in 5% of patients, complete remission (CR) was achieved (9). With the other antibody, MDX-060, in phase I/II trial, 72 patients with relapse/ refractory CD30-positive lymphomas were treated. The ORR was 6% in patients with HL and 29% in patients with ALCL (10). Besides the studies where these components were used as the monotherapy, the Cancer and Leukemia Group B (CALGB) tried to combine SGN-30 with the cytostatic combination GVD (gemcitabine, vinorelbine, liposomal doxorubicin) in the phase II trial (11). However, this study was prematurely closed due to development of grade 3-5 pneumonitis in 5 of 30 patients. The mechanism of pneumonitis occurrence is not entirely clear, but all five patients with pneumonitis had valin/fenilalanin polymorphism at Fc Gamma RIIIα gene, which points to the possible immunological mechanism of occurrence (11).

Brentuximab vedotin: symbiosis success

The unexpectedly low response of unconjugated anti-CD30 antibodies in the conducted studies, has led the investigators to further development of anti-CD30 drugs, in order to use CD30 receptor as the therapy target. Having in mind that the antibodies which bind to CD30 receptor are

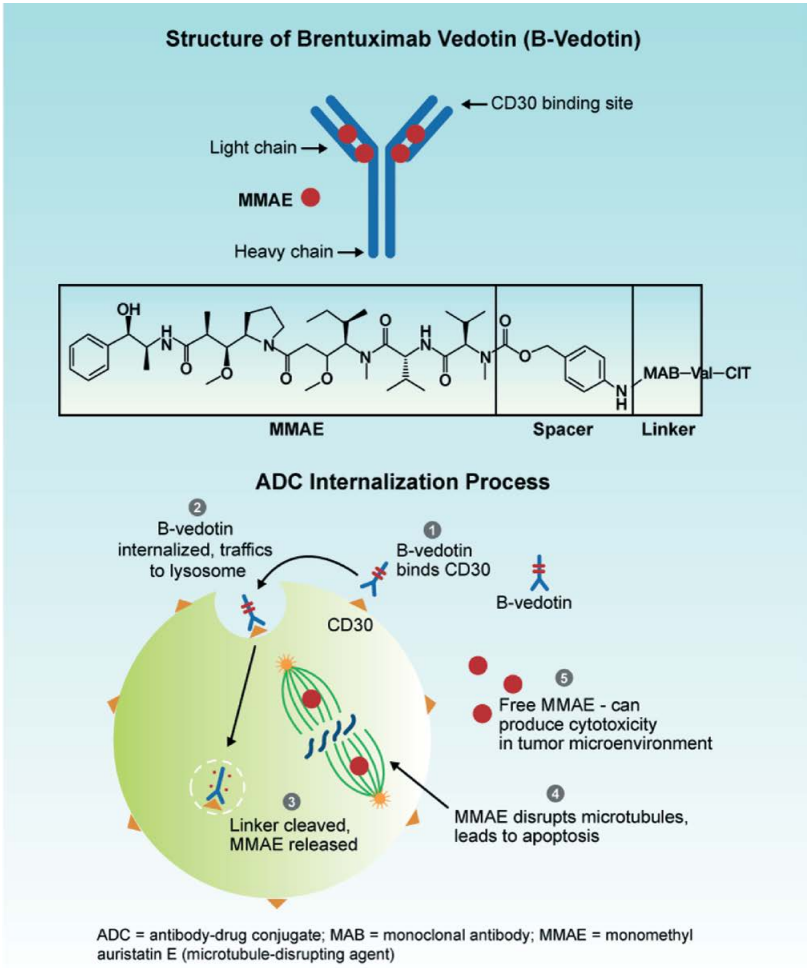

Figure 1. Brentuximab-vedotin mechanism of action (Taken from www.researchtopractice.com)

internalized in the endocytosomes, the binding of the cytotoxic drug with Fc fragment of the antibody, would enable that the cytostatic could be led precisely to the malignant cell, so that the high dose of such cytotoxic drug is directed to the lymphoma cells, without any significant effect to the other cells of the body (2). Brentuximab vedotin (BV) (SGN-35, Adcetris, TM, SeattleGenetics; Millenium, Takeda) is one of the best examples of such symbiosis of the antibody and the cytotoxic drug. It is synthesized when the already existing drug SGN-30, the monomethyl auristatin E (MMAE) was added. MMAE is the analog of dolastatin 10, the antimitotic substance. The BV mechanism consists of binding to CD30 receptor at the cell surface, after which this complex is internalized into the cell. The MMAE is then released in lysosome through proteolytic degradation. After that, the MMAE impedes the microtubule network in the cell, which leads to stoppage of the cell cycle in G2/M phase and the programmed cell death (12, 13) (Figure 1).

Clinical studies with brentuximab vedotin

After the testing at the cell lines, where it proved its potency (14), the clinical trials with BV were initiated. The first study of phase I/II in patients with relapse/refractory CD30-positive lymphoma included 45 patients (42 with HL, two with ALCL and one with angioimmunoblastic T-cell lymphoma. The patients were heavily pretreated, and 73% of patients had ASCT in the previous treatment. The primary goal was to define the drug dose, and the secondary, the response to treatment. Doses below 1.8mg/kg were well tolerated, while, at this dose level, 36% experienced weakness, 33% pyrexia, 22% of patients, peripheral neuropathy. With higher doses of 2.7mg/kg, 17% of patients experienced neutropenia of grade 3, while one patient, who received the dose of 3.6mg/kg developed febrile neutropenia and died from sepsis. However, the greatest problem regarding higher doses was the occurrence of peripheral neuropathies, which, although they spontaneously disappeared in 63% of patients, were the main limiting factor for definition of a higher dose, so the dose for the further studies remained at 1.8mg/kg. Six out of 12 patients, who were treated with this dose, had objective response to therapy, with median duration of 9.7 months (15). The other phase I study compared a weekly to a three-weekly regimen and the conclusion of this study was that a three-week dosing is more optimal, with similar toxicity profile as in the previously mentioned study (16). The first phase II study was published in 2010 at the annual meeting of the ASH (American Society of Hematology), and the results were updated at the ASCO 2011 (American Society of Clinical Oncology) meeting (17). The total number of 102 patients with relapse/refractory HL was included in the study. Median number of the previous therapies was four, while median age of the patients was 31 years. All patients previously underwent ASCT. The ORR was 75%, while in 34% of patients the CR was achieved. Median PFS was 5.6 months, while in patients who achieved complete remission, the median PFS was 20.5 months. After the follow up of more than a year and a half, 31 patients remained without progression (18).

In ALCL, a phase II study was also published at the ASCO 2011, and then updated in the Journal of Clinical Oncology. The total number of 58 patients was included in the study, the ORR was 86%, CR 53%, and the median survival was not achieved. Median PFS was 14.6 months (19).

The results of these studies accelerated registration procedure at the Food and Drug Administration (FDA), so BV was registered for the HL patients after ASCT or after two lines of conventional chemotherapy and for the relapse/refractory patients with ALCL (2).

Is there a possibility for progress?

Brentuximab vedotin showed significant results as monotherapy and raised several questions for its optimal administration in patients with CD30-posistive lymphoma. The first question that needs to be answered is whether it is possible to combine BV with chemotherapy and whether BV shall improve the chemotherapy results in newly diagnosed patients. Such phase I study was initiated, where BV was combined with ABVD or ABV protocols and the first interim results were published at the ASH 2011 (20). What was observed is that 28% of patients, who were administered ABVD, developed lung toxicity, similar to the CALGB study with GVD protocol (11). The study was continued with the AVD protocol, without bleomycin, in order to, possibly avoid lung toxicity. Similar study was initiated with GHSG (German Hodgkin Study Group) (21) which compared the classical escBEACOPP, with bEACOPP protocol, where bleomycin was replaced with BV.

The other study concept is the maintenance therapy after ASCT, in patients with HL with bad prognostic score at the moment of relapse. Such study is also ongoing under the name of AETHERA (22).

Finally, there is a question whether the patients who initially responded to BV, shall respond to the same drug in relapse. A small study (23), speaks in favor of this statement, but the trials of larger, randomized studies are necessary for more persuasive conclusion.

There are still wide possibilities for BV testing. There is a possibility to add BV to salvage and a high-dose protocol prior to or during ASCT. It is necessary to test the immunological and other mechanisms of lung toxicity and to find the optimal number of cycles, i.e. the duration of administration of this drug in patients with HL and ALCL.

CONCLUSION

The fact that BV is the first drug after 30 years, which was approved for treatment of HL, speaks in favor of the fact that we are the witnesses of revolution in treatment of these patients. Further clinical trial investigations will show whether BV shall take even more important position in treatment of HL and ALCL and whether it shall become "Mabthera" for HL and ALCL.

Conflict of interest

We declare no conflicts of interest.

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