

The Role of Reed-Sternberg CD30 Receptor and Lymphocytes in Pathogenesis of Disease and Its Implication for Treatment

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Hodgkin lymphoma is a cancer that can be cured using standard chemotherapy with or without radiation. Although it accounts for only 0.6% of all malignancy worldwide, but it usually affects young adults with median age of 38 years. About 60 to 90% cases can be cured depending on its stage and 5 to 10% cases are refractory to the first-line chemotherapy; while 20 to 30% patients experiencing relapse after receiving the first-line chemotherapy.¹ The relapse causes new problem in treatment. A monoclonal antibody-chemotherapy conjugate, Brentuximab vedotin, was approved by Food Drug Association and European Medicine since 2011 dan was approved by European Medicine Agency since 2012 to treat relapsed classical Hodgkin lymphoma and anaplastic large cell lymphoma (ALCL). Brentuximab vedotin has also been known as anti-CD30.²

CD30 or Ki-1 or TNFRSF8 is a 120-kD glycoprotein, which is a trans-membrane receptor of Hodgkin lymphoma cells. The glycoprotein was first identified in 1982 using monoclonal antibody against Hodgkin lymphoma-derived cell lines. The glycoprotein was then cloned and recognized as a member of tumor necrosis factor receptor (TNFR) superfamily, which has intracellular, transcellular and extracellular domains.^{3,4} The monoclonal antibody obviously does cause a reaction not only with the Reed-Sternberg (RS) cells of Hodgkin lymphoma, but also with a small number of normal lymphocytes subset, which are located at perifollicular zone

as well as lymphoid tumor such as anaplastic large cell lymphoma (ALCL) and other non-lymphoid tumor such as embryonic and pancreas carcinoma, undifferentiated nasopharyngeal carcinoma and malignant melanoma. Therefore, CD30 monoclonal antibody alone to confirm the diagnosis of Hodgkin lymphoma is ineffective as it must be used together with other panel of immunohistochemistry antibodies such as cytokeratins, carcinoma embryonic antigen, melanoma-associated antigen and placental alkaline phosphatide.^{5,6}

The expression of CD30 molecules in Reed-Sternberg cells of Hodgkin lymphoma has been demonstrated in over 98% of classical Hodgkin lymphoma cases; however, there is a difference in staining intensity among various cases or even in one case.⁶

In addition to the CD30, CD15 is also a very important marker for Hodgkin lymphoma / Reed-Sternberg (RS) cells and it is found in more than 80% of classical Hodgkin lymphoma cases. CD15 is a typical antigen for classical Hodgkin lymphoma; however, it is not specific as it is also found in T-cell and B-cell lymphoma as well as non-lymphoid tumor.⁶

The National Comprehensive Cancer Network (NCCN) and European Society Medical Oncology (ESMO) have recommended the test of both antigens for cases with suspected classical Hodgkin lymphoma.^{7,8} A study by Fadhil et al⁹ in Northern Iraq with 42 cases of classical Hodgkin lymphoma has demonstrated that 100% cases

have CD30 expression and only 51.8% cases have CD15 expression. A study in Indonesia by Ranuhardi et al, which is published in the present edition, has successfully demonstrated CD30 expression in 88.9% cases and CD15 expression in 37.5% cases of the studied 42 Hodgkin lymphoma cases. The study results indicate that Indonesia is ready to follow the current standard treatment guideline for relapsed classical Hodgkin lymphoma, which requires immunohistochemistry examination of CD30 as the target therapy of Brentuximab vedotin treatment along with the approval that has been issued by Indonesian National Agency of Drug and Food Control (NADFC) in late 2007.

Brentuximab vedotin acts by binding with the CD30 receptor at the surface of Hodgkin lymphoma/Reed-Sternberg cells, which then performs internalization with lysosome. Afterward, monomethyl auristatin E (MMAE) is released into proliferated tubulin cells and the apoptosis of Reed-Sternberg cells takes place.

Over-expression of CD30 is actually not only found in lymphoid and non-lymphoid malignant cases. It is also found in T lymphocytes of patients with systemic lupus erythematosus (SLE) particularly in CD8 of the T lymphocytes. There are ongoing clinical trials on the use of anti-CD30 for SLE. Moreover, the 88-kD soluble CD30 (sCD30), which is found in inflammatory condition is also associated with the activity of SLE disease.¹⁰

Shooshtarizadeh et al show that the high level sCD30 prior to transplantation is a risk factor for rejected renal transplantation.¹¹ Moreover, Susal et al also demonstrate that the high level of sCD30 prior to transplantation may have more significant implication on treatment of rejection after one-year renal transplantation and the risk of losing the graft is higher on 5-year follow up.¹² In Indonesia, Bonar et al provide a report in this edition that the one-year survival of graft and patients are 92% and 87%; while the 3-year survival are 90.6% and 79.7%. Amirzagar et al.¹³ showed that the high level of sCD30 prior to renal transplantation and the 1 week and 2 weeks post-transplantation is associated with poor graft survival.

In addition to malignancy and autoimmune cases, increased expression of CD30 is also

found in allergy cases such as asthma. Rojas et al¹⁴ demonstrated that there was increased CD30 expression of Th2 lymphocytes in children with atopic asthma. Meanwhile, Polte et al¹⁵ showed the role of interaction between CD30 receptor and its ligand (CD153) in inducing allergic asthma facilitated by Th2 cells. Foks et al¹⁶ suggested that there is a role of interaction between CD30 and CD30 ligand in the development of atherosclerosis. In their study, Foks et al gave antibody against CD30 ligand in mice that interrupted the interaction between CD30 and CD30 ligand, which then diminishing the initial development of atherosclerosis.

CD30, CD30 ligand and sCD30 have roles in the pathogenesis of malignant, autoimmune, allergy and metabolic disease. The three of them can be diagnostic, prognostic or therapeutic marker for classical Hodgkin lymphoma, cardiovascular disease, lupus erythematosus, asthma and allergy.

Brentuximab vedotin, which is the novel anti-CD30 has been recently approved as treatment for Hodgkin lymphoma and is still studied in ongoing clinical trials as treatment for systemic lupus erythematosus.¹⁷ It provides evidences of interconnection between basic medical science and clinical medicine in medical advance.

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