Current status of molecular targeted therapy for hematologic malignancies Introduction

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Molecular targeted drugs have been extensively introduced to pharmacotherapy in the field of cancer, including hematologic malignancies (Table). Compared with other solid tumors, one of the unique characteristics of hematologic malignancies is the marked chemosensitivity of neoplastic cells to conventional chemotherapy. So, before the era of molecular targeted therapy, hematologic malignancies such as acute lymphocytic leukemia in childhood, Burkitt's lymphoma / leukemia, and Hodgkin's disease were curable with conventional combination chemotherapy, and other hematologic malignancies such as acute myeloid leukemia, acute lymphocytic leukemia of adulthood, and some subsets of lymphoma were also relatively curable with conventional chemotherapy. Thus, the benefits of the introduction of molecular targeted agents for hematologic malignancies are clinically thought to be mainly classifiable into 3 categories: (1) Increase the cure rate of already chemotherapeutically curable malignancies. (2) Cure chemotherapeutically resistant malignancies. (3) Achieve some therapeutic effect (but not yet cure) against chemotherapeutically resistant malignancies.

In category (1), the representative is rituximab, a chimeric murine /

human anti-CD20 monoclonal antibody, for malignant lymphoma. Non-Hodgkin's lymphoma is curable with combination chemotherapy of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or a CHOP-like regimen. Much evidence has been reported that survival rates are significantly increased by the addition of rituximab to CHOP or a CHOP-like regimen in diffuse large B-cell lymphoma [1] and follicular lymphoma [2] patients. In category (2), there are drugs targeting abnormal molecules specific to neoplastic cells [3]. A series of *bcr-abl* tyrosine kinase inhibitors for chronic myeloid leukemia are commonly known [4]. Imatinib mesylate, a well-known first-generation drug, was initially reported as a molecular targeted drug synthesized pharmacogenomically that exhibited a marked antileukemic (antineoplastic) effect (approved in 2001 in the US). Other important issues regarding this kind of drug are its rapid synthesis and clinical application as second-and third-generation drugs for *bcr-abl* tyrosine kinase inhibitors (shown in parenthesis), which were synthesized to overcome imatinib resistance due to the emergence of mutant clones of *bcr-abl*. The second-generation drugs, dasatinib (in 2006) and nilotinib (in 2007) are effective for most mutant clones except T315I [5]. The

third-generation drug ponatinib (in 2012) is effective against mutants including T315I [5]. From now on, as a crucial matter, how to knock out CML stem cells should be extensively studied both basically and clinically. Also, several studies on how to stop tyrosine kinase inhibitors in the clinic are ongoing, which is important both clinically and economically. In category (3) are drugs for diseases including myelodysplastic syndrome (MDS) and multiple myeloma. Especially, MDS is a clonal hematopoietic stem cell disease for which no standard therapy exists. Recently, azacytidine, a cytidine analog which was synthesized in 1963, was focused on regarding its epigenetic effect as a demethylating agent by inhibiting DNA cytosine methylation and, as a result, increasing the expression of a suppressed gene. The drug is thought to be the first shown to be effective against myelodysplastic syndromes, significantly prolonging the survival of patients compared with a control [6].

In conclusion, currently, molecular targeted drugs synthesized pharmacogenomically may show marked effects such as cure against some of resistant cancers. Moreover, this kind of drug more effectively increases the survival rate and more rapidly improves the QOL compared with

conventional anticancer agents, and could be safer if administered by professional hemato-oncologists to patients with hematologic malignancies.

Conflict of interest. The author declares no conflict of interest.

References

1 .Coiffier B, Thieblemont C, Van Den Neste E, et al : Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients : a study by the Groupe d' Etudes des Lymphomes de l' Adulte. Blood 116 : 2040 – 2045, 2010

2. Marcus R, Imrie K, Solal - Celigny P, et al: PhaseⅢ Study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol 26 : 4579 - 4586, 2008

3. Ueda T : Update on molecular-targeted therapy in hematologic malignancies. Int J Clin Oncol 12 : 311 – 312, 2007

4. Baccarani M, Deininger MW, Rosti G, et al : European LeukemiaNet recommendations for the management of chronic myeloid leukemia : Blood 122 : 872 – 884, 2013

5. Cortes JE, Kantarjian H, Shah NP, et al : Ponatinib in refractory Philadelphia chromosome-positive leukemias. N Engl J Med 367 : 2075 –

2088, 2012

6. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al : Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol 10 : 223 -232, 2009