

# Ten Best Readings Relating to Chronic Myeloid Leukemia (CML)

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**Azam M, Seeliger MA, Gray NS, et al. Activation of tyrosine kinases by mutation of the gatekeeper threonine. *Nat Struct Mol Biol.* 2008;15(10):1109-1118. Epub 2008 Sep 14.**

Mutation of the gatekeeper threonine is a common mechanism of activation for tyrosine kinases and provides structural insights to guide the development of next-generation inhibitors.

**Lee SJ, Kukreja M, Wang T, et al. Impact of prior imatinib mesylate on the outcome of hematopoietic cell transplantation for chronic myeloid leukemia. *Blood.* 2008;112(8):3500-3507. Epub 2008 Jul 29.**

Among hematopoietic cell transplantation patients with advanced chronic myeloid leukemia, use of imatinib mesylate (IM) before hematopoietic cell transplantation was not associated with treatment-related mortality, relapse, leukemia-free survival, or survival. Acute graft-versus-host disease rates were similar between IM(+) and IM(-) groups regardless of leukemia phase.

**de Lavallade H, Apperley JF, Khorashad JS, et al. Imatinib for newly diagnosed patients with chronic myeloid leukemia: incidence of sustained responses in an intention-to-treat analysis. *J Clin Oncol.* 2008;26(20):3358-3363. Epub 2008 Jun 2.**

Imatinib is highly effective in most patients with chronic myeloid leukemia in chronic phase; patients who respond are likely to live substantially longer than those treated with earlier therapies. Achieving complete cytogenetic response correlated with progression-free survival and overall survival, but achieving major molecular response had no further predictive value.

**Wang Y, Cai D, Brendel C, et al. Adaptive secretion of granulocyte-macrophage colony-stimulating factor (GM-CSF) mediates imatinib and nilotinib resistance in BCR/ABL+ progenitors via JAK-2/STAT-5 pathway activation. *Blood.* 2007;109(5):2147-2155. Epub 2006 Nov 7.**

Inhibition of janus kinases 2 (JAK-2) overcomes granulocyte-macrophage colony-stimulating factor-induced imatinib mesylate and nilotinib progenitor cell resistance, providing a rationale for the application of

JAK-2 inhibitors to eradicate residual disease in chronic myeloid leukemia.

**Bewry NN, Nair RR, Emmons MF, et al. Stat3 contributes to resistance toward BCR-ABL inhibitors in a bone marrow microenvironment model of drug resistance. *Mol Cancer Ther.* 2008;7(10):3169-3175.**

These data support a novel mechanism of BCR-ABL-independent imatinib mesylate resistance and provide preclinical rationale for using Stat3 inhibitors to increase the efficacy of imatinib mesylate within the context of the bone marrow microenvironment.

**Tam CS, Kantarjian H, Garcia-Manero G, et al. Failure to achieve a major cytogenetic response by 12 months defines inadequate response in patients receiving nilotinib or dasatinib as second or subsequent line therapy for chronic myeloid leukemia. *Blood.* 2008;112(3):516-518. Epub 2008 May 20.**

These results suggest that patients receiving second-line tyrosine kinase inhibitor (2TKI) with no cytogenetic response at 3 to 6 months should be considered for alternative therapies.

**Quintarelli C, Dotti G, De Angelis B, et al. Cytotoxic T lymphocytes directed to the preferentially expressed antigen of melanoma (PRAME) target chronic myeloid leukemia. *Blood.* 2008;112(5):1876-1885. Epub 2008 Jun 30.**

Preferentially expressed antigen of melanoma cytotoxic T lymphocytes (PRAME CTLs) were generated almost exclusively from the naive T-cell compartment, and clonal analysis showed these cells could have high TCR-peptide avidity. PRAME CTLs or vaccines may be of value for patients with chronic myeloid leukemia.

**Yong AS, Keyvanfar K, Eniafe R, et al. Hematopoietic stem cells and progenitors of chronic myeloid leukemia express leukemia-associated antigens: implications for the graft-versus-leukemia effect and peptide vaccine-based immunotherapy. *Leukemia.* 2008;22(9):1721-1727. Epub 2008 Jun 12.**

Surface expression of WT1 protein in the most primitive hematopoietic stem cells in advanced-phase

chronic myeloid leukemia suggests that they could be targets for WT1 peptide-based vaccines, which in combination with preferentially expressed antigen of melanoma (PRAME), could additionally improve targeting differentiated progeny and benefit patients responding suboptimally to tyrosine kinase inhibitors, or enhance graft-versus-leukemia effects in stem cell transplantation patients.

**Maslak PG, Dao T, Gomez M, et al. A pilot vaccination trial of synthetic analog peptides derived from the BCR-ABL breakpoints in CML patients with minimal disease. *Leukemia*. 2008;22(8):1613-1616. Epub 2008 Feb 7.**

This trial suggests that although it is possible to immunize patients with chronic myeloid leukemia (CML) against their own breakpoint peptides, there may be insufficient processing or presentation of the appro-

priate peptides on the cell surface of target CML cells or a T-cell response that is too weak to allow for clinically relevant activity, even in the setting of minimal disease.

**Chen CI, Maecker HT, Lee PP. Development and dynamics of robust T-cell responses to CML under imatinib treatment. *Blood*. 2008;111(11):5342-5349. Epub 2008 Mar 7.**

Antileukemia T-cell responses develop in the majority of chronic myeloid leukemia (CML) patients (9 of 14) in remission, and CD4(+) T cells producing tumor necrosis factor- $\alpha$  (median 17.6%) represent the major response over interferon- $\gamma$ . This confirms the immune system's ability to respond to leukemia under certain conditions. Such responses may be further amplified as a potential therapy that synergizes with imatinib for improved control of CML.