Reinforced molecular targeted therapy for Ph+ Leukemias based on risk-benefit assessment

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Scope of the lecture:

To provide updated information of current therapy for Ph+ leukemias, especially focusing on third- generation tyrosine kinase inhibitor

Learning objectives:

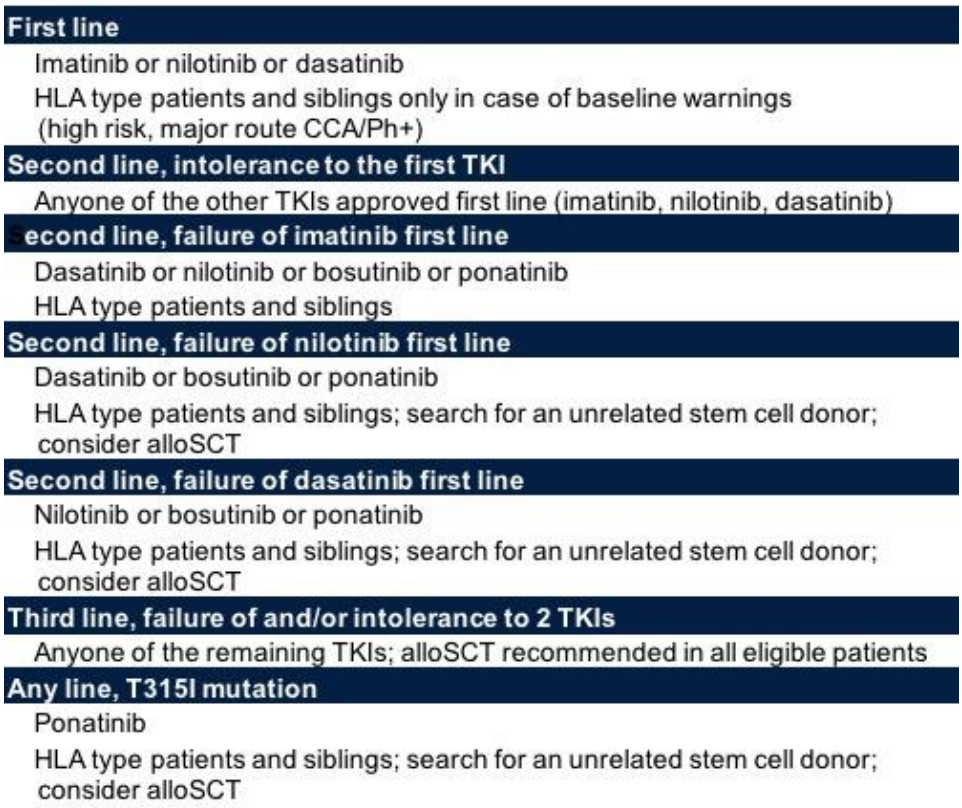
1. The point for differential usage of currently available TKIs according to the guidelines
2. The role of 3rd generation TKI, ponatinib, in the management of Ph+ leukemias
3. The proper use of ponatinib based on risk-benefit assessment of patients

Extended abstract:

The Philadelphia chromosome (Ph), a small derivative from reciprocal translocation between the long arms of chromosomes 9 and 22, is detected in >90% of chronic myeloid leukemia (CML) and 20-30% of adult acute lymphoblastic leukemia (ALL). The Ph chromosome results in formation of the BCR-ABL1 fusion gene, which encodes a constitutively active protein tyrosine kinase. Without treatment and even with conventional chemotherapy, CML generally progresses within several years from a stable chronic phase (CP) to an accelerated phase (AP), and terminates in a terrible blastic phase (BP). Ph+ ALL is a most aggressive form of ALL and carries a poor prognosis comparable to BP-CML.

ABL tyrosine kinase inhibitors (TKIs) have dramatically improved the prognosis of patients with Ph-positive (Ph+) leukemias icluding CML and Ph+ALL, and three generations of TKIs are currently available according to the clinical settings defined by newly diagnosed disease, resistant and/or intolerant diseases to prior TKIs: imatinib (first-generation; 1G), nilotinib, dasatinib, bosutinib (second-generation; 2G), and ponatinib (third generation; 3G) (**Figure 1** from ***Blood 2013 122:872-84***).

Figure 1



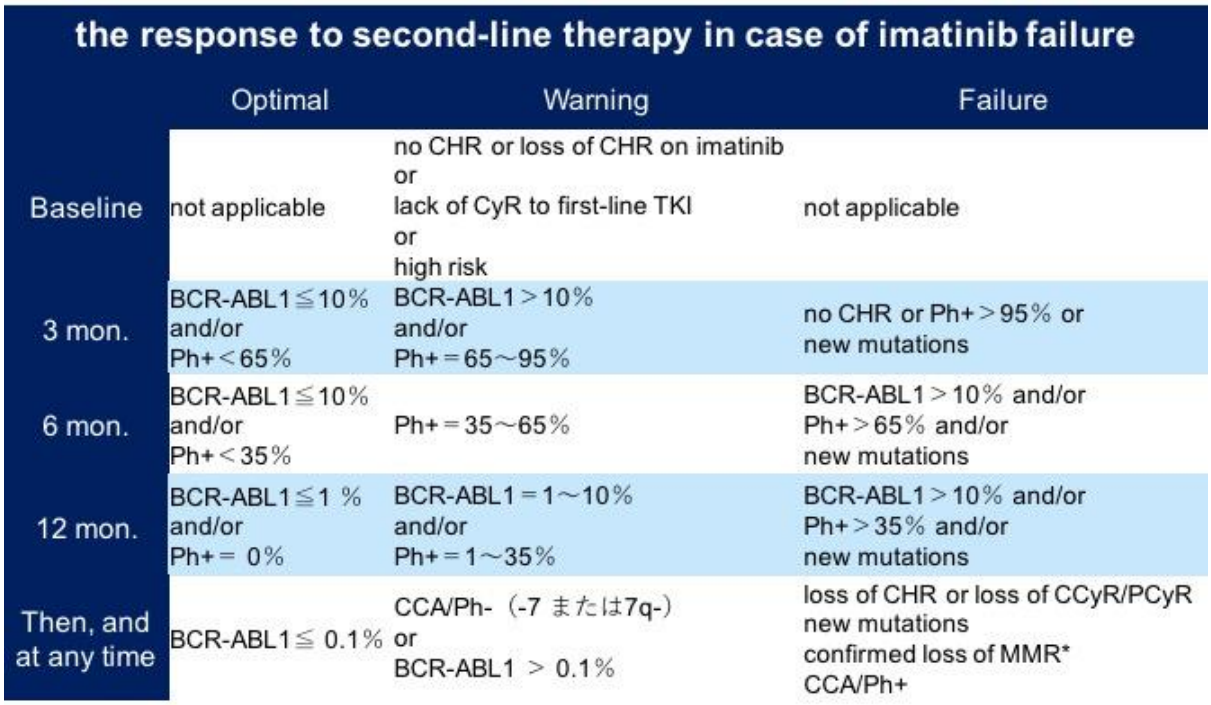
Periodic molecular monitoring of peripheral blood BCR-ABL1 transcripts using quantitative RT-PCR on international scale (BCR-ABL1^{IS}) allows us to make a better choice among these TKIs according to the guidelines from the European Leukemia Net (ELN) (**Figure 2 & 3** from ***Blood 2013 122:872-84***) and/or the National Comprehensive Cancer Network (NCCN).

Figure 2

the response to TKIs (any TKI) as first-line treatment

	Optimal	Warning	Failure
Baseline	not applicable	high risk or CCA/Ph +	not applicable
3 mon.	BCR-ABL1^{IS}≦10% and/or Ph+≦35%	BCR-ABL1^{IS}>10% and/or Ph+=36～95%	non-CHR and/or Ph+>95%
6 mon.	BCR-ABL1^{IS}≦1 % and/or Ph+=0%	BCR-ABL1^{IS}=1～10%, and/or Ph+=1～35%	BCR-ABL1^{IS}>10% and/or Ph+>35%
12 mon.	BCR-ABL1^{IS}≦0.1%	BCR-ABL1^{IS}=0.1～1%	BCR-ABL1>1% and/or Ph+>0%
Then, and at any time	BCR-ABL1^{IS}≦0.1%	CCA/Ph- (-7 or 7q-)	loss of CHR, loss of CCyR, confirmed loss of MMR* mutations, CCA/Ph+

Figure 3



MMR, BCR-ABL1 ≥0.1% = MR3.0 or better; CCA/Ph+, clonal chromosome abnormalities in Ph+ cells; CCA/Ph–, clonal chromosome abnormalities in Ph– cells.

* In 2 consecutive tests, of which one with a BCR-ABL transcripts level ≥1%.

Although outcomes for patients with newly diagnosed CML improved following the introduction of imatinib, some patients can develop resistance to imatinib. Second-line options for imatinib-resistant disease include imatinib (high-dose), dasatinib, nilotinib, or bosutinib. 2G TKIs are more potent than imatinib and inhibit many imatinib-resistant point mutants and native BCR-ABL1, but all 4 TKIs (imatinib, dasatinib, nilotinib, bosutinib) are ineffective against the BCR-ABL1 gatekeeper mutation, T315I.

Ponatinib is a 3G oral TKI with potent activity against native and mutated BCR-ABL1, including T315I and other recurrent mutations. In Japan, based on the results of domestic Phase I/II study (NCT01667133), as well as the US Phase I and international Phase II PACE trials, ponatinib is approved for the treatment of patients with CML resistant/intolerant to preceding drug treatment, or patients with relapsed or treatment-resistant Ph+ ALL. In Japanese clinical trial, major cytogenetic response (MCyR) by 12 months was achieved/maintained in 65% of CP-CML patients resistant/intolerant to nilotinib or dasatinib, and major hematologic response (MaHR) by 6 months was achieved in 61% of patients with advanced phase disease resistant/intolerant to prior TKIs. While this study was in progress, accumulation of an emerging arterial occlusive event (AOE) safety signal was reported with

longer follow-up across the ponatinib clinical program, and dose reduction from 45 or 30 mg/day to 30 or 15 mg/day was instructed, respectively. Overall, AOEs were reported in 5 (14%) patients; 3 (18%) patients with CP-CML and 2 (11%) with advanced phase disease. No grade 5 AOEs were reported (***Int J Hematol. 2017*** *doi: 10.1007/s12185-017-2238-9*).

Multivariate analysis from a pooled population of ponatinb clinical trial patients indicates dose intensity, history of ischemic disease and age were the strongest independent predictors of increased risk of AOE, and that prediction of an approximately 33% reduction in the risk of AOE for each 15 mg/day decrease in average ponatinib dose intensity. In addition, dose-intensity was also strongly associated with pancreatitis, rash, cardiac failure (***Leuk Res. 2016 48:84-91***).

Thus, ponatinib, a current final weapon for Ph+ leukemias, should be administered properly through risk-benefit assessment of individual patients (**Figure 4**). Several TKIs have a narrow therapeutic range and were known to have large inter-individual variations according to acidity of gastric absorption, and possible detoxification based on genetic polymorphisms of metabolic enzymes and drug-drug interactions. These oral TKIs are candidates for therapeutic drug monitoring (TDM) due to their high inter-individual variability for therapeutic and toxic effects. Although TDM is already being used for imatinib in clinical practice, additional studies are required to improve this practice with the inclusion of other TKIs, especially ponatinib.

Figure 4