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BETing on rational combination therapy in mutant *FLT3* acute myeloid leukemia

Richard M. Stone

Leukemia Division, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

E-mail: RICHARD M. STONE - rstone@partners.org

doi:10.3324/haematol.2020.274753

Acute myeloid leukemia (AML) is a heterogenous largely intrinsically resistant bone marrow stem cell malignancy.[1] While intensive therapies, including stem cell transplant, can cure some patients, these are difficult to apply and/or are ineffective in the many older patients who contract this disease. Individual patients have varying degrees of sensitivity to available agents which can be delineated based on cytogenetic and molecular disease features. About 30% of AML patients have malignant cells whose DNA harbors a mutation in the *FLT3* gene, encoding a transmembrane tyrosine kinase that transmits mitogenic signals from the extracellular space to the nucleus.[2] Three-quarters of the mutations encode a duplication of from 3 to 100 amino acids in the juxtamembrane region (which is associated with an adverse prognosis); the remaining mutations are point mutations in the tyrosine kinase domain.[2] Both mutations result in spontaneous dimerization and activation of the enzyme without the need for cognate ligand binding. Patients with mutant *FLT3* AML are routinely treated in the upfront setting with chemotherapy plus midostaurin, a multitargeted tyrosine kinase with FLT3 inhibitory activity.[3] Patients with relapsed or refractory mutant *FLT3* AML can be treated with gilteritinib, a more specific and relatively well-tolerated FLT3 inhibitor, based on results of a clinical trial showing superior survival with gilteritinb compared to conventional chemotherapy.[4]

Unfortunately, despite the successes with midostaurin and gilteritinib in clinical trials, patients with mutant *FLT3* AML frequently relapse after such therapies and are thus in need of new agents. The study of the mechanisms of resistance to FLT3 inhibitory therapy in AML is an important strategy to derive additional therapies. Patients who fail to respond or relapse after responding to gilteritinib frequently have mutations in the RAF-MAP-ERK downstream pathway.[5] While there are no inhibitors of this pathway in use for leukemia, this would be one strategy to employ in combination with FLT3 inhibitors to forestall or eliminate such resistance. Levis and colleagues have suggested that bromodomain inhibition in combination with FLT3 inhibition could potentially be a useful way to overcome resistance to single-agent FLT3 inhibitory therapy (*M Levis, personal observations, 2020*).

Bromodomain and extra-terminal domain (BET proteins) are master transcriptional regulators which activate a wide variety of genes[6] that are involved in cell cycle progression, leukemogenesis, and elaboration of stromal derived cytokines, the latter being important mechanisms of resistance to FLT3 inhibitors.[7] FLT3 inhibitors often clear peripheral blasts but fail to eliminate bone marrow blasts, presumably due to these pro-survival cytokines. Thus, inhibition of BET proteins, including BRD 2, 3 and 4 and BRD T could be useful in preventing FLT3 inhibitor resistance. BRD 4 may be the most relevant target since it recruits an important complex involved in transcription of MYC and other genes important in promoting cell division; this complex is called the positive transcription elongation factor complex (P-TEFb).

In this edition of Haematolgica, Lee *et al.* show that a novel BET inhibitor, PLX51107, achieved the goal of adequate MYC suppression in humans, thereby making it an attractive agent to combine with FLT3 inhibitors.[8] Could MYC downregulation with its associated decrease in cell cycle progression be useful in combination with FLT3 inhibitors such as the FLT3 ITD specific and potent agent, quizartinib?

Lee *et al.* make the important point that, while previous work had demonstrated synergistic cytotoxic effect of the BET inhibitor JQ1 and a FLT3 inhibitor, these experiments were performed in cell suspension culture which fails to faithfully reproduce the clinical situation. Blasts preferentially survive in the bone marrow stroma bathed in cytokines released by endothelial and other support cells. The authors of the current work showed that PXL51107 has single-agent activity against the FLT3 ITD containing human leukemia cell lines MV4-11 and MOLM14 in culture and *in vivo* in murine xenograft models but has no independent FLT3 inhibitory activity. This activity was synergistically increased when quizartinib was given in combination in the MV4-11 xenograft model or in primary AML cells co-cultured with bone marrow stroma. Further, plasma samples obtained from patients on a clinical trial of single-agent PLX51107 display MYC inhibition activity, suggesting that this agent possesses the requisite properties to achieve the goal of downregulation of pro-survival cytokines, making it a good candidate to combine with FLT3 inhibitors.

In summary, the preclinical work described by Lee *et al.*

supports an eventual trial of a BET inhibitor in combination with a FLT3 inhibitor in patients with mutant *FLT3* AML.[8] The idea is to injure the malignant cells with a FLT3 inhibitor and deprive them of their 'comfort zone' with the BET inhibitor. With an increase in potentially useful molecules in AML, the solid pre-clinical studies such as those described by Lee *et al.*[8] are needed to choose the most potentially useful combinations for clinical use.

Disclosures

RMS has sat on ad hoc boards and has had a consultancy role for Hoffman-LaRoche, Pfizer, Otsuka, Novartis, Jazz, Celgene, Astellas, Arog, Amgen, Agios, Actinum, Abbvie, Takeda, Macrogneics, Janssen, Gemoab, Daichii-Sanko, Biolinerx, Trovagene, Stemline, AStraZeneca, Elevate Bio, BerGenBio, Foghorn, Innate Pharma. GSK, Syndax, and Syros. He has been Principal Investigator for clinical research of his institution with Agios, Abbvie, Syndax, and Lilly. He has sat on the Data Safety and Monitoring Board for Celgene, Takeda, Argenix, and Syntax Clinical.

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