Clinical response to upfront targeted tyrosine kinase inhibitors among patients with myeloid and lymphoid neoplasms with eosinophilia and rearrangements

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Background

Recently renamed myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusion (MLN-TK) included a heterogeneous group of rare cancers. Other than in PDGFRA chronic phase disease, the outcomes of tyrosine kinase inhibitors are not well known in other rarer TK genes and blast phase. Here, we aimed to determine the response to and the long-term outcomes of upfront TKI therapy compared to upfront chemotherapy alone.

Methods

We retrospectively reviewed the medical records of 42 patients diagnosed with MLN-Eo with PDGFRA, PDGFRB, FGFR1, JAK2, or FLT3 rearrangement at Moffitt Cancer Center (MCC), Duke Cancer Center, and the University of California at San Francisco (UCSF) Medical Center between July 2010 and July 2021. Patients were divided to two groups based on a morphologic classification of the disease at diagnosis: chronic phase and *de novo* blast phase.

- **primary objectives**

> **chronic-phase:** assess the time-to-blast-phase (TTBP) transformation, calculated from the diagnosis until the time of transformation to acute leukemia or the last follow-up date.

> **de novo blast-phase:** estimate the overall survival (OS), which was calculated from the time of diagnosis of blast-phase or transformation to the time of death or censored to the last follow-up

Result

TKI was effective at controlling the chronic-phase disease with gene fusion other than PDGFRA

Among 25 patients in chronic-phase disease at the diagnosis, 15 (60%) received frontline TKIs targeted to their fusion gene. 12 patients with PDGFRA fusion received imatinib. 2 patients with PDGFRB received imatinib, and 1 with FGFR1 fusion received ponatinib. Like PDGFRA fusion, none of the patients with PDGFRB or FGFR1 fusion treated with TKI transformed into blast-phase disease. Among the remaining 10 patients who did not receive upfront TKI therapy, including 4 with PDGFRA, 5 (50%) transformed to blast-phase disease (AML or ALL) at the median follow-up of 73 months. The median time to blast phase was 45 months.

Upfront TKI is critical in obtaining remission in *de-novo* Blast-phase disease.

Among 16 (40%) patients presenting with blast-phase disease, 9 patients (56%) with de novo blast-phase disease received upfront TKI therapy alone (n=3) or with chemotherapy (n=6). All 9 patients achieved CR and remained alive at a median follow-up of 20 months. Two patients with FLT3::ETV6 rearrangement were treated with quizartinib and gilteritinib; 5 patients with PDGFRA/B rearrangement were treated with imatinib (n=4) and midostaurin (n=1); 3 patients with FGFR1 fusion were treated with ponatinib (n=2) and pemigatinib (n=1). The patient treated with midostaurin also had a coexisting FLT-ITD mutation.

The other 7 patients received induction chemotherapy without TKI therapy. Among these patients, the median OS was 29 months. Three patients received salvage TKI therapy, with all three deaths due to progressive disease.

Figure 1. Patients' distribution

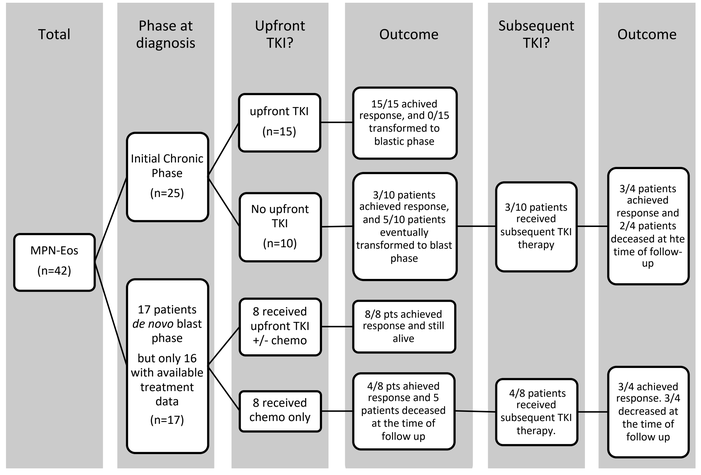


Table 1 Prognostics factors of OS among patients with MLN-Eo.

	Univariate		Multivariate	
Predictor	**HR**	**95% CI**	**HR**	**95% CI**
Male	2.14	(0.62, 7.38)	3.6	(0.70, 18.85)
Age	1.03	(0.19, 1.78)	1.03	(0.97, 1.09)
Hypereosinophilia in peripheral blood	0.58	(0.16, 1.2)	1.3	(0.19, 8.4)
PDGFRA/B abnormalities	0.33	(0.10, 1.10)	0.53	(0.08, 3.6)
Complex cytogenetic at diagnosis	2.06	(0.44, 9.60)	0.91	(0.09, 9.27)
Blast-phase at initial diagnosis	1.89	(0.56, 6.35)	0.81	(0.16, 4.22)
Upfront TKI therapy	0.054	(0.007, 0.42)	0.03	(0.002, 0.47)
Received alloHSCT	1.42	(0.46, 4.38)	0.30	(0.06, 1.6)

Abbreviations: alloHSCT, allogeneic hematopoetic cell transplant; CI, Confidence interval, HR, hazard ratio; MLN-Eos, myeloid and lymphoid neoplasms with eosinophilia; OS, overall survival; TKI, tyrosine kinase inhibitor.

Summary

Our cohort showed the excellent long-term outcome of upfront TKI therapy for patients with MLN-TK in non-PDGFRA chronic and blast phase disease. However, TKIs were less effective in the relapsed setting. The potential mechanisms need to be further elucidated.

Discussion

Upfront TKI therapy alone or with chemotherapy can provide excellent disease control in the blast phase. In our study, all patients in the de-novo blast phase achieved CR after upfront TKI therapy, and the remission appeared to be sustained even in the absence of alloHSCT. On the contrary, intensive induction therapies without TKI resulted in progression or relapse, Subsequent TKI after intensive chemotherapies appeared to be less effective. Some patients developed longitudinal changes of additional cytogenetics abnormalities, which suggest the clonal evolution of the malignant cells after intensive chemotherapies. We hypothesize that initiating driver fusion occurs in hematopoietic stem cells or pluripotent progenitors. As such, chemotherapy is unlikely to induce sustained response because of the quiescent features in hematopoietic stem cells. Instead, under the stress of the high-intensity chemotherapy, the malignant/premalignant genetically rearranged cancer stem cells, instead of dying from the chemotherapy, increase their plasticity to promote senescence escape and acquire additional mutations, rendering them less responsive or even resistant to subsequent TKI therapy. (27) Only upfront TKI therapy can interrupt the tyrosine kinase signaling and suppress or eradicate the malignant precursor MLN-TK clones.