Background

Internal tandem duplication (ITD) or point mutations of the Fms-like tyrosine kinase 3 (FLT3) are present in approximately 30% of patients with acute myeloid leukemia (AML) (Thiede et al., 2002). The ITD mutation is associated with very poor disease prognosis (Kottaridis et al., 2003) and additional acquired mutations of FLT3, including the D835 or the "F691" mutation, have been identified in patients who harboring dual ITD plus D835/F691 mutations, which is apparently mediated through suppression of FLT3/BTK/AurK and their downstream signaling pathways. We evaluated the anti-leukemia effect of CG’806 in leukemia cell lines harboring FLT3 ITD and TKD mutations, and further in a murine leukemia model engrafted with murine BaF3-FLT3-ITD cells. In addition, we investigated combinatorial regimens with Bcl-2 family inhibitors for enhancing the anti-leukemia effects of CG’806 against FLT3-mutated AML.

Materials and Methods

Cell Lines: BaF3 cells harboring FLT3 wt type (WT), ITD mutations and/or TKD domain mutations were used for evaluating anti-leukemia effects of CG’806, an oral, small molecule multi-kinase inhibitor of BTK/FLT3/AurK.

Results

CG’806 Exerts Effective Anti-leukemia Effects in Both FLT3 Mutant and Wild Type Leukemia Cell Lines, and Primary AML Samples As Well

Conclusions

- CG’806 is effective in both FLT3 WT and mutant AML cells, including those harboring dual ITD plus D835/F691 mutations, which is apparently mediated through suppression of FLT3/BTK/AurK and their downstream signaling pathways.
- CG’806 Exerts pro-apoptotic effects in primary AML cells, but not in normal bone marrow cells.
- CG’806 significantly reduces disease burden, circulating blasts, and extends survival in a dose-dependent manner in BaF3-ITD-engrafted murine AML model.
- FL or BM stromal cells do not protect AML cells from CG’806-induced cell killing.
- Concomitant blockade of FLT3, Bcl-2 and/or Mcl-1 induces synergistic pro-apoptotic effects in FLT3-mutant leukemia cells including those resistant to quizartinib.

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