Dasatinib enhances the expansion of CD56\(^+\)CD3\(^−\) NK cells from cord blood

Dasatinib can inhibit T-cell activation through inhibition of the Scr family of tyrosine kinases such as p56 (Lck).\(^1\) It has been reported that some chronic myeloid leukemia (CML) patients who were treated with dasatinib developed chronic large-granular lymphocytosis (LGL) with natural killer (NK) or NK T-cell lineage, and that these patients achieved optimal molecular response.\(^2\) In addition, Mustjoki et al reported clonal expansion of NK T cells during dasatinib therapy.\(^3\) Kreutzman et al reported that mono/oligoclonal T and NK cells were present in CML patients at diagnosis and expanded during dasatinib therapy and that LGL expansion is linked to cytomegalovirus infection.\(^4,5\) Therefore, dasatinib may have a favorable effect on NK-cell proliferation. In this study, we analyzed the effects of dasatinib on the expansion of NK cells from cord blood and transcriptional factors during expansion.

Umbilical cord blood cells (1 \(×\) 10\(^6\)/mL; Hokkaido Cord Blood Bank) were cultured with IL-15 (10 ng/mL; PeproTech), IL-2 (5 ng/mL; R&D Systems), and anti-CD3 mAb (OKT3, 10 ng/mL; Janssen Pharmaceutical); with or without dasatinib (10nM; a kind gift from Bristol-Myers Squibb) in culture medium stem cell growth medium (CeeGenix) with 5% human AB serum in 24-well plates, as we reported previously.\(^6\) After a 7-day culture of umbilical cord blood cells (1 \(×\) 10\(^6\)/mL), the absolute number of CD56\(^+\)CD3\(^−\) NK cells had significantly increased in the culture with dasatinib compared with the culture with cytokines only (5.96 \(±\) 3.95 vs 0.81 \(±\) 0.62, \(P < .05\); Figure 1C).

At present, there are only a few transcription factors that are known to play an essential role in NK-cell development, especially in humans. T-box proteins, T-bet, and Eomes are involved in NK-cell development.\(^7,9\) T-bet and Eomes are both later required for the differentiation in DX5\(^+\)(CD49b) CD11b\(^+\) NK cells. In addition, Eomes is highly expressed in fully differentiated NK cells. In this study, we showed NK-cell expansion after culture with dasatinib and increased expression of Eomes after 24 hours. Therefore, dasatinib has some role in NK-cell expansion from cord blood under the condition of IL-2 and IL-15 stimulation through increased expression of transcription factors such as Eomes. This observation may have potentially important implication for the treatment of other diseases with dasatinib.\(^10\)

References


Conflict-of-interest disclosure: The authors declare no competing financial interests.

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References


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