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Title: Effect of tyrosine kinase inhibitors, imatinib and nilotinib, in murine lipopolysaccharide-induced acute lung injury during neutropenia recovery

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Body: Neutrophil recovery has been implicated in deterioration of oxygenation and exacerbation of preexisting acute lung injury (ALI). The aim of this study was to investigate whether imatinib or nilotinib was effective on lipopolysaccharide (LPS)-induced ALI during neutropenia recovery in mice. ICR mice were rendered neutropenic with cyclophosphamide prior to the intratracheal instillation of LPS. Imatinib or nilotinib was administrated by oral gavage during neutropenia recovery. In order to study the effects of drugs, mice were killed on day 5 and blood, bronchoalveolar lavage (BAL) fluid and lung tissue samples were obtained. The lung wet/dry (W/D) weight ratio and protein levels in the BAL fluid or lung tissue were determined. Treatment with imatinib or nilotinib significantly attenuated the LPS-induced pulmonary edema, and this result was supported by the histopathological examination. The concentrations of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6 and myeloperoxidase (MPO) in BAL fluid were significantly inhibited by imatinib or nilotinib in mice of ALI during neutropenia recovery. The mRNA expressions of platelet-derived growth factor receptor (PDGFR)-β and c-kit in imatinib or nilotinib group were significantly lower than LPS group. Our data indicated that imatinib or nilotinib effectively attenuated LPS-induced ALI during neutropenia recovery. These results provide evidence for the therapeutic potential of imatinib and nilotinib in ALI during neutropenia recovery. To our knowledge, this is the first study evaluating the effects of tyrosine kinase inhibitors in a mouse model of ALI during neutropenia recovery.