ABSTRACT

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Acute myeloid leukemia (AML) is an aggressive cancer with a poor prognosis for which therapy failure is often responsible. Development of drug resistance is among the most common causes of treatment failure. The exact mechanisms leading to the resistance are not known, especially for drugs recently introduced into the clinical practice such as gilteritinib. Therefore, the gilteritinib-resistant leukemic cell line (referred to as HL-60 g75) has been established in our lab and further characterized. The aim of this study was to evaluate the sensitivity of HL-60 g75 cells to gilteritinib and to clarify the stability of acquired resistance. We revealed that the resistance of HL-60 g75 cells is transient, since only after 4 weeks of gilteritinib-free cell culture, sensitivity of these cells was restored. While gilteritinib induced apoptosis similarly in both gilteritinib-sensitive (HL-60 wt) and -resistant cells, cell cycle analysis revealed lower responsiveness of HL-60 g75 to gilteritinib than HL-60 wt. Furthermore, sensitivity of HL-60 g75 to midostaurin and sunitinib, drugs with similar mechanism of action as gilteritinib, was established. HL-60 g75 showed cross-resistance to sunitinib, but not to midostaurin. Given the physicochemical similarities between gilteritinib and sunitinib, and the fact that sunitinib resistance results from lysosomal sequestration, we decided to test the possible association of lysosomes and gilteritinib. Cell lines were stained with LysoTracker,a lysosome-specific dye, which revealed a higher median fluorescence intensity (MFI) of LysoTracker in HL-60 g75 than HL-60 wt. On the contrary, cell exposure to sunitinib showed lower MFI in HL-60 g75 suggesting alterations of lysosomal pH, involvement of efflux transporters or saturation

of lysosomes. Nevertheless, further experiments will have to be performed to fully uncover cellular mechanisms leading to gilteritinib resistance.