

The Aurora-A inhibitor MLN8237 affects multiple mitotic processes and induces dose-dependent mitotic abnormalities and aneuploidy

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ABSTRACT

Inhibition of Aurora kinase activity by small molecules is being actively investigated as a potential anti-cancer strategy. A successful therapeutic use of Aurora inhibitors relies on a comprehensive understanding of the effects of inactivating Aurora kinases on cell division, a challenging aim given the pleiotropic roles of those kinases during mitosis. Here we have used the Aurora-A inhibitor MLN8237, currently under phase-I/III clinical trials, in dose-response assays in U2OS human cancer cells synchronously proceeding towards mitosis. By following the behaviour and fate of single Aurora-inhibited cells in mitosis by live microscopy, we show that MLN8237 treatment affects multiple processes that are differentially sensitive to the loss of Aurora-A function. A role of Aurora-A in controlling the orientation of cell division emerges. MLN8237 treatment, even in high doses, fails to induce efficient elimination of dividing cells, or of their progeny, while inducing significant aneuploidy in daughter cells. The results of single-cell analyses show a complex cellular response to MLN8237 and evidence that its effects are strongly dose-dependent: these issues deserve consideration in the light of the design of strategies to kill cancer cells via inhibition of Aurora kinases.