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Regulation of Subcellular Location and Activity of Cdc2-CyclinB1 is Involved in Bendamustine-induced G2 Arrest

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***SUMMARY*. Bendamustine is a multifunctional alkylating agent for the treatment of multiple myeloma, with the G2/M arrest-induction ability in human multiple myeloma RPMI-8226 cells, but the mechanism remains ambiguous. In this study, we found bendamustine caused the G2 arrest in 24 h, regulated the phosphorylation status of Cdc2, and blocked the nuclear import of Cdc2-CyclinB1 complex. Pretreatment with ATM/ATR inhibitor caffeine or p38 MAPK inhibitor SB203580 suppressed the phosphorylation of Cdc2 at Thr14/Tyr15 or attenuate the blockade of nuclear import, respectively; however, neither of these two inhibitors nor the combination imposed significant effects on Bendamustine-triggered G2 arrest. Bendamustine-induced blockade of the nuclear translocation dissipated after 48 h, after which, the G2 arrest was maintained through the inhibitory phosphorylation of Cdc2. Taken together, our research suggested that two or more pathways and mechanisms which regulated the cell cycle in a time-dependent manner were involved in the G2 arrest invoked by bendamustine.**

KEY WORDS: Bendamustine, Cdc2-CyclinB1 complex, G2 arrest, RPMI-8226.

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