

The cytotoxic effects of bendamustine in combination with cytarabine in mantle cell lymphoma cell lines

Carlo Visco, Silvia Castegnaro, Katia Chieragato, Martina Bernardi, Elena Albiero, Cristina Zanon, Domenico Madeo, Francesco Rodeghiero

Abstract

Bendamustine is clinically useful in mantle-cell lymphoma (MCL). Its favorable toxicity profile in vivo favors its combination with other cytotoxic drugs. Cytarabine is a key drug in the treatment of younger patients with MCL. The current study investigated the in-vitro cytotoxic effect of bendamustine and cytarabine, alone or combined, on two MCL cell lines representing the classic and blastoid variant of the lymphoma subtype (JEKO-1 and GRANTA-519). Cell lines were exposed to each drug alone, or simultaneously and consecutively to both drugs, for different time schedules. Apoptosis was measured by flow cytometry. Mitochondrial damage, cell proliferation/metabolic activity, and cell cycle analysis were also assessed. The synergistic, additive, or antagonistic effects of the drugs were calculated with the combination index (CI) method. Bendamustine and cytarabine alone exhibited relevant cytotoxic activity on both cell lines. Both drugs induced cell cycle arrest in S phase. Drug combinations were associated with significantly higher cytotoxic effects than each drug alone. Among the combination schedules, the consecutive incubation of bendamustine followed by cytarabine was associated with the lower CI, being 10-100-fold lower than with simultaneous incubations. The cytotoxic effect of the consecutive combination was prominent on both cell lines, indicating a very strong and highly significant synergy in inducing apoptosis. Similar results were obtained measuring mitochondrial damage or the decline of the metabolic activity in all cell lines. The strong synergistic effect of bendamustine and cytarabine on MCL cells provides a rationale for developing schedules combining these agents in the treatment of MCL.