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Original Article

Y-320, a novel immune-modulator, sensitizes multidrug-resistant tumors to chemotherapy

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Abstract: Y-320, a novel immune-modulator, inhibits IL-17 production by $CD4^+$ T cells stimulated with IL-15. Its use in autoimmune diseases such as rheumatoid arthritis has been documented. However, no studies have be conducted to evaluate its application in cancer treatment either as mono or combined therapy. This study demonstrated that while Y-320 had little effect on multidrug resistance (MDR) cell lines, it induced remarkable injury to MDR tumor cells when concurrently administered with other chemotherapeutic agents. Concomitant use of Y-320 with a low dose of paclitaxel significantly sensitized MDR tumors by inducing G2/M phase arrest and apoptosis. Further analyses indicated that Y-320 was a substrate of P-glycoprotein (P-gp). It could inhibit P-gp efflux function without altering P-gp expression, and subsequently reverse P-gp mediated drug resistance in MDR cells. The co-administration of Y-320 and paclitaxel suppressed tumor growth remarkably with an inhibition rate of 77.1% compared to 6.5% in the paclitaxel monotherapy group *in vivo*. This co-treatment did not increase extra complications in MDR tumor xenograft models. Particularly, no significant changes in body weight and hepatorenal serology were observed with the co-treatment. In conclusion, our results confirm that Y-320 is a promising chemotherapy sensitizer for the first time. The co-administration of Y-320 and chemotherapeutic agents might be an effective and low-toxicity chemotherapeutic regime for the MDR tumor patients.

Keywords: Y-320, multidrug resistance, P-glycoprotein, chemotherapy sensitizer, combined therapy

Introduction

Chemotherapy is one of the most widely used methods for treating malignant tumors. However, the extensive use of these agents in the clinic has resulted in a growing number of problems. Multidrug resistance (MDR) and the associated complications related to drug toxicity are of particular concern. Although high doses of chemotherapeutic agents play a remarkable role in killing tumors, they often induce many complications such as myelosuppression, weight loss, gastrointestinal dysfunction, nervous system dysfunction, cardiopulmonary dysfunction, hepatic and renal dysfunction. These undesirable effects have negatively impacted clinical treatment countermeasures for malignant and metastatic tumors. Alternatives such as low-dose multi-cycle therapeutic plan can mitigate these adverse reactions but can lead to drug resistance in tumors, further desensitizing these cells. As a result, balancing the effectiveness and low-toxicity of these agents is critical in the area of clinical research.

1-(4-chlorophenyl)-N-[3-cyano-4-(4-morpholinopiperidin-1-yl)phenyl]-5-methylpyrazole-4-carboxamide (Y-320), a novel phenylpyrazoleanilide immunomodulator [1, 2], can inhibit the synthesis of interleukin-17 (IL-17) in $CD4^+$ T cells [2]. IL-17 is an inflammatory cytokine with powerful pro-inflammatory properties, mediating various autoimmune diseases through diverse