Latin American Journal of Pharmacy
(formerly *Acta Farmacéutica Bonaerense)*
Lat. Am. J. Pharm. **36** (6): 1250-4 (2017)

Received: March 21, 2017
Accepted: March 26, 2017

Ovarian Cancer Treatment Drug Everolimus Inhibits the Metabolic Elimination of First-Line Anti-Colon Cancer Irinotecan

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***SUMMARY*. Ovarian cancer remains to the top severe disease to threaten the health of women, and everolimus is the drug clinically used to treat ovarian cancer. Due to the high frequency of colon cancer resulted from the cancer metastasis, irinotecan might be co-administered with everolimus. This study aims to determine the drug-drug interaction (DDI) between everolimus and irinotecan. *In silico* docking method was employed to dock everolimus into the activity cavity of UDP-glucuronosyltransferase (UGT) 1A1 which catalyzes the glucuronidation of irinotecan's active metabolite SN-38. The chemical structure of everolimus was drawn, and homology modeling was used to construct the crystal structure of UGT1A1. The activity cavity of UGT1A1 binding with everolimus was consisted of the following amino acids residues: Asp11, Gly12, Ser13, Trp15, Leu16, Ser40, Leu41, Tyr42, Asp45, Ala47, Phe48, Leu51, Val68, His72, Val74, Phe75, Glu76, Asn77, Asp78, Ser79, Phe80, Leu81, Gln82, Arg83, Ser284, Met285, Val286, Arg311, Thr313, Gly314, Thr315, Lys328, Leu330, and Gln332. The hydrophobic interaction contributes to the strong binding capability of everolimus with the activity cavity of UGT1A1, and the amino acids residues contributing to this hydrophobic interaction contained Asp11, Gly-12, Leu41, Tyr42, Asp45, Val68, Glu76, Leu81, Arg83, Ser284, Gly314, Thr315, and Lys328. In conclusion, everolimus-irinotecan interaction might occur during the treatment of ovarian cancer with co-administration of everolimus and irinotecan.**

RESUMEN. El cáncer de ovario continúa siendo la enfermedad más grave que amenaza la salud de las mujeres, y everolimus es el fármaco utilizado clínicamente para tratar el cáncer de ovario. Debido a la alta frecuencia de cáncer de colon resultante de la metástasis del cáncer, el irinotecán podría ser co-administrado con everolimus. Este estudio tiene como objetivo determinar la interacción fármaco-fármaco (DDI) entre everolimus e irinotecán. Se empleó el método de acoplamiento *in silico* para acoplar everolimus en la cavidad activa de UDP-glucuronosiltransferasa (UGT) 1A1 que cataliza la glucuronidación del metabolito activo de irinotecan SN-38. Se dibujó la estructura química de everolimus y se usó el modelado de homología para construir la estructura cristalina de UGT1A1. La cavidad activa de la unión de UGT1A1 con everolimus consistió en los siguientes residuos de aminoácidos: Asp11, Gly12, Ser13, Trp15, Leu16, Ser40, Leu41, Tyr42, Asp45, Ala47, Phe48, Leu51, Val68, His72, Val74, Phe75, Glu76 , Asn77, Asp78, Ser79, Phe80, Leu81, Gln82, Arg83, Ser284, Met285, Val286, Arg311, Thr313, Gly314, Thr315, Lys328, Leu330, y Gln332. La interacción hidrofóbica contribuye a la fuerte capacidad de unión de everolimus con la cavidad de actividad de UGT1A1 y los residuos de aminoácidos que contribuyen a esta interacción hidrófoba contienen Asp11, Gly12, Leu41, Tyr42, Asp45, Val68, Glu76, Leu81, Arg83, Ser284, Gly314, Thr315 y Lys328. En conclusión, la interacción everolimus-irinotecan puede ocurrir durante el tratamiento del cáncer de ovario con co-administración de everolimus e irinotecán.

KEY WORDS: drug-drug interaction, everolimus, *in silico* docking, irinotecan, ovarian cancer, UDP-glucuronosyltransferase (UGT) 1A1.

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ISSN 0326 2383 (printed ed.)
ISSN 2362-3853 (on line ed.)