substrates for both efflux pumps and the cytochrome p-450 A34 metabolizing enzyme. P-glycoprotein inhibitors also inhibit cytochrome P-450 enzymes that metabolize anticancer agents, thus leading to increased toxicity when they are co-administered with these agents.

This is particularly so with the first- and second-generation P-glycoprotein inhibitors. For example, Ebert *et al.* demonstrated that the co-administration of the P-glycoprotein inhibitor erythromycin and cardiac glycosides (digoxin) in hospitalized patients was associated with increased serum concentration of the latter.[58]Wakasugi*et al.* had earlier shown that clarithromycin increased the plasma concentration of co-administered digoxin by inhibition of P-glycoprotein–mediated renal excretion.[59] Verapamil and reserpine increased the cytotoxicity of taxols, anthracyclines, and vinca alkaloids by inhibition of P-glycoprotein–mediated efflux.[60]

The second-generation P-glycoprotein inhibitor valspodar inhibited the P-450 3A4-mediated metabolism of paclitaxel and vinblastine, resulting in an increased serum concentration of these agents.[61] This often necessitated a reduction in doses of anticancer agents with attendant reduction in clinical response.

These older-generation P-glycoprotein inhibitors also inhibit physiological efflux pumps such as those involved in blood–brain barrier, BTB, and placental functions.[62]

Generally, third-generation P-glycoprotein inhibitors exhibit a decreased incidence of toxicity when co-administered with other drugs.[49,63] Thus, tariquidar, laniquidar, and zosuquidar do not affect cytochrome P-450 3A4 at relevant concentrations; also, they do not affect physiological efflux pumps.[64]

Efflux pump inhibitors also exhibit adverse effects not related to efflux pump or the cytochrome P-450 enzyme function. Such effects include arrythmias (verapamil), immunosuppression (cyclosporin A), vaginal bleeding (tamoxifen), allergic hepatitis (ketoconazole), and cholestatic hepatitis (erythromycin).

Conclusion

Efflux pump-mediated mechanisms contribute to resistance in chemotherapy. As promising as efflux pump inhibitors appear to be, none has been approved for routine clinical use as a result of doubtful clinical efficacy and unacceptably high incidence of adverse effects. At present, their applications are mainly restricted to epidemiological studies. These drawbacks, notwithstanding, the search for efficacious and tolerable pump inhibitors continues because of the potential benefits. With such an agent, most chemotherapeutic agents rendered useless by efflux-mediated resistance will become useful again.

Way forward

a. Consider efflux pump substrate selectivity in the design and development of novel chemotherapeutic agents.
b. Structural elucidation of efflux pumps will help to develop more effective / specific inhibitors.
c. There is a need to screen natural herbs for efflux pump inhibitory activity.

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