resistance to doxorubicin, daunorubicin, vincristine, etoposide, epirubicin, chlorambucil, methotrexate (98, 99), melphalan, and paclitaxel, ABCC2 may confer resistance to doxorubicin, etoposide, methotrexate, irinotecan (SN-38), vincristine, vinblastine, camptothecin, paclitaxel, docetaxel, etoposide, and cisplatin, and ABCC4 may confer resistance to rubitecan and irinotecan.

b. Biology of Cross-Resistance

Cross-resistance refers to the situation where treating a patient with a first drug confers changes in the physiology of the tumor that reduce the efficacy of a second, unrelated drug that may be administered at a later time (100).

Cross-resistance can result from the situation where the first drug induces expression of one of the ABC transporters, and where this particular ABC transporter pumps the first drug out of the tumor cell, and also pumps a second drug out of the tumor cell, for example, a second drug administered at some later time in a clinical trial.

In making clinical decisions on the administration of different sequences of drugs, caution should be used when faced with information revealing that a first drug induces resistance to a second drug, by way of stimulating the activity of a drug transporter. Also, caution should be used in the situation where the first drug is hydrophilic and the second drug is hydrophobic, and caution should be used where the first drug is a large molecule and the second drug is a small molecule (101).

Also, greater credence should be given to a well-controlled study of drug resistance in actual human subjects, than to a well-controlled study with cultured cells. The ultimate arbiter of appropriate trial design is whether the therapy actually works—many attempts to use drug sequences that were configured to avoid resistance have often failed to be effective (102).

c. A Tumor's Genetic Expression Can Provide Guidance on Drug Resistance

Gene expression data from a tumor can determine whether the tumor is likely to be resistant to a given drug (103, 104).

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