k. Drug Resistance as a Basis for Exclusion

Prior treatment with a specific chemotherapeutic drug may be in the list of exclusion criteria, where the basis is drug resistance (resistance to both the earlier drug and the study drug). Resistance can arise from the fact that the earlier-administered drug induces genetic changes in the chromosomes of tumors, for example, changes in expression of drug transporters and changes that are mutations in oncogenes.

Resistance to a drug does not necessarily mean that the tumor had experienced a genetic change. Resistance can also present when a tumor is heterogeneous, for example, where it contains two types of cancer cells, where the first type is chemosensitive but the second type is chemoresistant. Koletsis et al. (91) observed that, at least in the context of lung cancer, non-responsiveness to chemotherapy can result where tumors are heterogeneous, that is, where lung tumors are a mixture of cells with the histology of small-cell lung cancer and non-small-cell lung cancer.

II. BIOCHEMISTRY OF DRUG RESISTANCE

a. Biochemistry of the ABC Drug Transporters

During chemotherapy against tumors, most drugs target proteins or nucleic acids that are located inside the tumor cell. Unfortunately, tumors have a number of transport systems that are able to pump drugs back out of the tumor cell. O'Brien et al. (92) and Burtness et al. (93) describe a number of drug transporters. One of these transport systems is a system called the ABC transporters. As reviewed by Elliott and Al-Hajj (94), the human genome encodes nearly 50 ABC transporters. Of these transporters, those used for multidrug transport are listed below.

In the following list of drug transporters, the alternate names are disclosed, for example, ABCC1 is the same protein as MRP1:

MRP1/ABCC1; MRP2/ABCC2; MRP3/ABCC3; MRP4/ABCC4; MRP5/ABCC5; MRP6/ABCC6; MRP7/ABCC10; MRP8/ABCC11; and MRP9/ABCC12 (95).

According to various publications (96, 97), the transporter known as ABCC1 may confer

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