

Table 4.2 Cumulative toxicity^a

Drug	Cumulative toxicity
Cisplatin	Renal toxicity; neurotoxicity; high-tone hearing loss
Carboplatin	Thrombocytopenia
Paclitaxel	Peripheral neurotoxicity
Etoposide	Leukemia
Doxorubicin	Palmar-plantar erythrodysesthesia (PPE), cardiotoxicity
Gemcitabine	Cardiotoxicity, pulmonary toxicity, thrombotic microangiopathy
Topotecan	No cumulative toxicity

^aDunton CJ. Management of treatment-related toxicity in advanced ovarian cancer. *The Oncologist*. 2002; 7(suppl 5):11–19.

Table 4.2 documents the cumulative and irreversible toxicities of some commonly used oncology drugs.

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. (73) 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. BIOLOGY 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. (74) and Burtness et al. (75) describe a number of drug transporters. One of these transport

⁷³ Koletsis EN, Prokakis C, Karanikolas M, Apostolakis E, Dougenis D. Current role of surgery in small cell lung carcinoma. *J Cardiothorac Surg*. 2009;4:30.

⁷⁴ O'Brien C, Cavet G, Pandita A, et al. Functional genomics identifies ABCB3 as a mediator of taxane resistance in HER2-amplified breast cancer. *Cancer Res*. 2008;68:5380–5389.

⁷⁵ Burtness BA, Manola J, Axelrod R, et al. A randomized phase II study of ixabepilone (BMS-247550) given daily × 5 days every 3 weeks or weekly in patients with metastatic or recurrent squamous cell cancer of the head and neck: an Eastern Cooperative Oncology Group study. *Ann Oncol*. 2008;19:977–983.