In the non-small-cell lung cancer clinical trial of Ramlau et al. (86), the inclusion criteria required that all study subjects had received standard chemotherapy prior to enrolling in the Ramlau study. But this prior chemotherapy proved to be an issue during the analysis of adverse events that were captured during the Ramlau study. Ramlau's study drug was topotecan, a drug not known to cause neuropathy. But some of the topotecan-treated subjects had the adverse event of neuropathy. The authors attributed this neuropathy to chemotherapy received prior to entering the clinical trial, writing, "[b]ecause topotecan is not known to cause neuropathy, the neuropathy reported by patients in this group (8% topotecan vs 26% in the docetaxel group) is likely from first-line therapy or the malignant process itself."

Radiation can produce irreversible toxicity, for example, to the heart. Billingham et al. (87, 88) document the fact that radiation treatment can cause irreversible damage to the heart where, upon administering chemotherapy many years later, a cumulative effect is produced. These authors report that, "[t]his study indicates that radiation, even if remote, enhances adriamycin-induced cardiomyopathy. Therefore, adriamycin must be given cautiously in patients who have received previous mediastinal radiotherapy."

TABLE 4.2 Cumulative Toxicity[b]

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

[b]*Dunton CJ. Management of treatment-related toxicity in advanced ovarian cancer. The Oncologist. 2002;7 (Suppl. 5):11–9.*

Cumulative toxicity refers to a situation where previous chemotherapy has been given, and more is contemplated at a later date, and where the toxicities of the earlier and later treatments are additive (89).

The above considerations provide a basis for inclusion criteria requiring that subjects be treatment-naive, and why some inclusion criteria stipulate the dose level of previous chemotherapy which must not have been exceeded (90).

The following table documents the cumulative and irreversible toxicities of some commonly used oncology drugs (Table 4.2).

[86]Ramlau R, Gervais R, Krzakowski M, et al. Phase III study comparing oral topotecan to intravenous docetaxel in patients with pretreated advanced non-small-cell lung cancer. J. Clin. Oncol. 2006;24:2800–7.

[87]Billingham ME, Bristow MR, Glatstein E, Mason JW, Masek MA, Daniels JR. Adriamycin cardiotoxicity: endomyocardial biopsy evidence of enhancement by irradiation. Am. J. Surg. Pathol. 197;1:17–23.

[88]Bird BR, Swain SM. Cardiac toxicity in breast cancer survivors: review of potential cardiac problems. Clin. Cancer Res. 2008;14:14–24.

[89]Barrett-Lee PJ. E-mail of October 12, 2010.

[90]Barrett-Lee PJ. E-mail of October 12, 2010.