Toxicity to the immune system encompasses a variety of adverse effects. These include suppression or enhancement of the immune response. Suppression of the immune response can lead to decreased host resistance to infectious agents or tumor cells. Enhancing the immune response can exaggerate autoimmune diseases or hypersensitivity. Drug or drug-protein adducts might also be recognized as foreign and stimulate an anti-drug response. Subsequent exposures to the drug can lead to hypersensitivity (allergic) reactions.

d. Dose modification

The following shows how to anticipate adverse events that are likely to occur during the course of the clinical trial. In anticipating these adverse events, the medical writer includes instructions for *dose modifications*.

Clinical trials can include dose modifications that *reduce dosing*, as detailed below, but also dose modifications that *increase dosing*. Increased dosing was used, for example, in the following clinical trial on leukemia. Where a starting dose of 400 mg imatinib per day was found to produce only partial response, the dose was increased to two 400 mg imatinib doses per day (19). *Dose escalations* have also been used, for example (20) in clinical trials of non-small cell lung cancer (21) breast cancer (22) and colorectal cancer (23) with the goal of improving drug efficacy against the cancer. Where an unanticipated need arises to increase dosing, and if the Protocol provides no guidance for increased dosing, the Protocol will likely need to be amended to allow for the increased dose. Bander et al. (24) provide an example of a dose-increasing amendment. Amending the Clinical Study Protocol requires approval by the Institutional Review Board (IRB) and the FDA.

The following concerns the more common type of dose modification, namely, dose reduction. Dose modification encompasses dose reduction and delays in administering doses subsequent to an intolerable adverse event. In clinical trials involving cytotoxic drugs, it is useful to include instructions in the Clinical Study Protocol for reducing or delaying the dose, in the event that a drug-related adverse event occurs. Where drug-related adverse events are detected in the course of a clinical trial, the presence of a

[19] O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2003;348:994–1004.

[20] These examples were found by inputting the search term "could be escalated."

[21] Schiller JH, Larson T, Ou SH, et al. Efficacy and safety of axitinib in patients with advanced non-small-cell lung cancer: results from a phase II study. *J Clin Oncol*. 2009;27:3836–3841.

[22] O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol*. 2002;20:2812–2823.

[23] Van Cutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. *J Clin Oncol*. 2001;19:4097–4106.

[24] Bander NH, Milowsky MI, Nanus DM, et al. Phase I trial of ^{177}lutetium-labeled J591, a monoclonal antibody to prostate-specific membrane antigen, in patients with androgen-independent prostate cancer. *J Clin Oncol*. 2005;23:4591–4601.