r. Methodology tip – bevacizumab and VEGF

Bevacizumab, known by the trade name of Avastin®, is an antibody that binds to a cytokine. This cytokine is vascular endothelial growth factor (VEGF). VEGF stimulates angiogenesis, that is, the growth of blood vessels. Bevacizumab blocks the action of VEGF, and in doing so prevents the genesis of new blood vessels that might ordinarily bring nutrients to tumors. The antibody is used for treating a variety of cancers (80).

s. Dose escalation – the Moore schema

For many small molecule drugs used in chemotherapy, it is assumed that the higher the dose, the more effective will be the anti-tumor treatment (81). Hence, the goal of Phase I dose-escalation clinical trials is to determine the highest tolerable dose. The adverse events that are measured are used to define the *dose-limiting toxicity* (DLT). The dose-limiting toxicity informs the investigator which dose is the *maximally tolerable dose* (MTD).

In a clinical trial of solid tumors, Moore et al. (82) administered increasing levels of drug (sorafenib) to different groups of patients (Fig. 2.17). Totally different groups of patients received each particular dose. It was never the case that one patient received one particular dose and, at a later point in the trial, was tested with a higher dose of the same drug. This dose-escalating trial followed a typical and conventional design of dose-finding trials.

According to Lin and Shih (83) the goal of dose-escalating Phase I clinical trials is to find the highest tolerable dose, as it is believed that maximal benefit to the patient can be achieved at this dose. This generalization applies to small molecules used in oncology. Once the Phase I trial is completed, the investigator then uses the maximally tolerable dose (MTD), or one dose below the MTD, as the recommended dose for a subsequent Phase II trial. This approach to finding the optimal dose is not used for biologicals, such as antibodies and cytokines, or to drugs for infections, immune disorders, or metabolic diseases. (It should be noted that it is common medical practice, when treating infections, immune disorders, and metabolic diseases, for the physician to increase dosing when a lower dose is not effective.)

In the Moore study, increasing sorafenib doses were as follows:

- 50 mg every 4 days;
- 50 mg every other day;

[80] Midgley R, Kerr D. Bevacizumab – current status and future directions. *Ann Oncol*. 2005;16:999–1004.

[81] Postel-Vinay S, Arkenau HT, Olmos D, et al. Clinical benefit in Phase-I trials of novel molecularly targeted agents: does dose matter? *Br J Cancer*. 2009;100:1373–1378.

[82] Moore M, Hirte HW, Siu L, et al. Phase I study to determine the safety and pharmacokinetics of the novel Raf kinase and VEGFR inhibitor BAY 43-9006, administered for 28 days on/7 days off in patients with advanced, refractory solid tumors. *Ann Oncol*. 2005;16:1688–1694.

[83] Lin Y, Shih WJ. Statistical properties of the traditional algorithm-based designs for phase I cancer clinical trials. *Biostatistics*. 2001;2:203–215.