



Figure 2.7 Schema showing 2-arm study. Subjects in the first arm received chemotherapy before as well as after surgery. Subjects in the second arm also received chemotherapy prior to and after surgery. The neoadjuvant chemotherapy in arm A was concurrent; that in arm B was sequential

CMF refers to the combination of three drugs, cyclophosphamide, methotrexate, and 5-fluorouracil.

e. Forwards sequence and reverse sequence – the Puhalla schema

The clinical trial of Puhalla et al. (38) contains two arms (Fig. 2.8). Subjects in the first arm received drugs in this order: D followed by AC. In detail, subjects received docetaxel on the first day of each cycle, for 4 cycles, where each cycle was 14 days long. This was followed by doxorubicin (an anthracycline drug) plus cyclophosphamide, on the first day of each cycle, for 4 cycles. Each cycle was 2 weeks long.

Now, this is about the second arm. Subjects in the second arm received drugs in the reverse order, that is, AC followed by D. The investigators chose a 2-arm study design, where each arm was the reverse of the other, because it was not possible to predict which order would provide the better outcome.

The type of trial design, where one arm uses a “forward sequence” of two drugs, and where another arm uses the “reverse sequence” of the two drugs, sometimes finds a basis in the mechanism of action of certain drugs. The following specifically concerns chemotherapy involving paclitaxel and gemcitabine. As explained by Paccagnella et al. (39) for a clinical trial on lung cancer, “[s]everal reports have shown that the sequence of administration of gemcitabine and paclitaxel may also affect the efficacy of this combination chemotherapy, since paclitaxel increases the concentration of active metabolite of gemcitabine (dFdCTP) when administered first.”

³⁸ Puhalla S, Mrozek E, Young D, et al. Randomized phase II adjuvant trial of dose-dense docetaxel before or after doxorubicin plus cyclophosphamide in axillary node-positive breast cancer. *J Clin Oncol.* 2008;26:1691–1697.

³⁹ Paccagnella A, Oniga F, Bearz A, et al. Adding gemcitabine to paclitaxel/carboplatin combination increases survival in advanced non-small-cell lung cancer: results of a phase II–III study. *J Clin Oncol.* 2006;24:681–687.