While all clinical trials have inclusion criteria and exclusion criteria, whether they be in oncology, infectious diseases, immune disorders, the clinical trial of Dy et al. (66) is unique in that the schema clearly identifies one of the inclusion criteria. The criterion shown in the flow chart is positive expression of c-kit.

Once enrolled in the trial, patients received repeated cycles of imatinib, each cycle lasting 28 days, for a total time of 16 weeks. Imaging was obtained after every other 28-day cycle, where imaging provided data on tumor size and number.

o. Methodology tip – c-kit and imatinib

The following concerns c-kit and imatinib. C-kit is a membrane-bound protein that has tyrosine kinase activity (67). The ligand of c-kit is stem cell factor. In other words, c-kit is the receptor of stem cell factor. Binding of stem cell factor to c-kit activates various cell-signaling pathways that are needed for proliferation, differentiation, and survival. Mutations in c-kit that increase the signaling activity of c-kit occur in various cancers, for example acute myeloid leukemia, gastrointestinal tumors, testicular cancer, and melanoma. Where the tumor contains a mutation in c-kit, the result is reduced survival, compared to patients bearing tumors having normal c-kit. Imatinib, an inhibitor of tyrosine kinase, has proven to be dramatically successful in treating a variety of cancers.

p. Run-in period – the Hanna schema

The run-in period of Hanna et al. (68) took the form of a miniature clinical trial where the goal was to determine if patients would respond favorably to a combination of three drugs (Fig. 2.15).

The three drugs were etoposide, ifosfamide, and cisplatin. After treatment with these three drugs during the run-in period, the patient's tumors were measured to determine tumor size and number. Where tumor size and number remained constant, or where tumors shrank, patients were then enrolled in the clinical trial, randomized, and assigned to arm A and arm B. But where the combination of the three drugs failed to control tumors, the patient was excluded from further study.

As shown in the schema (Fig. 2.15), patients with tumors controlled by the three drugs were randomized and assigned to arm A (control arm) where patients received no other drug, or to arm B, where patients received etoposide (study drug arm).

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[67] Roberts KG, Smith AM, McDougall F, et al. Essential requirement for PP2A inhibition by the oncogenic receptor c-KIT suggests PP2A reactivation as a strategy to treat c-KIT+ cancers. *Cancer Res*. 2010;70:5438–5447.

[68] Hanna NH, Sandier AB, Loehrer Sr. PJ, et al. Maintenance daily oral etoposide versus no further therapy following induction chemotherapy with etoposide plus ifosfamide plus cisplatin in extensive small-cell lung cancer: a Hoosier Oncology Group randomized study. *Ann Oncol*. 2002;13:95–102.