Performing Phase III Clinical Trials: Never an Easy Task

Every oncologist who has ever been involved in the design and coordination of a randomized phase III trial will appreciate the many problems and pitfalls that are associated with such a project. To name only a few: the recruitment of an adequate number of participating centers, the design of the trial in order to assure meaningful results and to reach agreement on this within a large group of investigators, quality control of the data, the pressure of other planned or ongoing trials within the same patient population. Yet we (should) prefer our day-to-day practice to be based on data from preferably two independent, high-quality phase III studies. If we agree on this, we should also accept as a consequence that any self-respecting institute should participate in and commit to these trials in order to allow these to be finished within a reasonable time and therefore provide relevant data.

In this issue, Dencausse et al. [1] present the data of a three-arm phase III study comparing 5FU + levamisole for 12 months (arm A) with 5FU + leucovorin for 12 months (B) and 6 months (C), as adjuvant treatment in stage III colon cancer. This study nicely illustrates several of the aspects mentioned above. First of all, the primary question of this study was perfectly relevant at the time the study was initiated in 1993. Due to a slow accrual, which probably resulted in part from preliminary data of other studies, the study was terminated after 5 years with less than half of the planned patients included. For a common type of cancer, this is a quite disappointing result, especially when 40 institutions had originally signed up, as is stated in the publication. Since this implies an average accrual of less than one patient per year per institution, one wonders why the remaining stage III colon cancer patients in each institution were not included and how they were treated. Obviously this implies a significant patient selection bias which invalidates the study results. Second, a more basic question relates to the design of the study. The authors designed the study in such a way that a *difference* between arm A and B, and at the same time *equivalence* between arm B and C should be detected. This is a highly unusual, if not inappropriate statistical design.

Aside from other comments one can make on the statistical paragraph of the paper, the two major problems are the primary endpoint and the number of planned patients. It is generally accepted that overall survival is the *only* relevant endpoint for adjuvant studies that include potentially toxic treatments. Possible exceptions may be relatively non-toxic and easy-to-administer treatments, such as currently used experimental vaccines, for which a significant increase in progression-free survival would be acceptable as the only benefit. Then, an appropriate number of patients should be planned in order to allow the detection of a statistical significant benefit in overall survival. Clearly, planning of only 150 patients in each of the 3 treatment arms does not meet this goal. Although concessions sometimes can be made for uncommon types of cancer, this certainly does not apply for stage III colon cancer. In this very same disease the pitfall of an inadequate study size has recently been demonstrated for the adjuvant use of the monoclonal antibody edrecolomab. Although the original trial (comparing edrecolomab treatment with observation) was conducted appropriately, only 166 eligible patients were available for analysis [2]. Based on the positive result of this trial, edrecolomab was approved for this indication in Germany. Yet when this treatment was subjected to a more rigorous test, involving 900 patients in each treatment arm, edrecolomab proved to be inferior to 5FU/leucovorin in terms of overall survival [3], upon which the use of edrecolomab has been terminated. Obviously this implies that a large number of patients may have received an inferior treatment during several years, and that a significant amount of healthcare money has been wasted. Therefore, the conclusions of the authors of the trial under discussion that arm B and C are equivalent and that the data do not indicate any differences overall simply cannot be made on the basis of the number of either planned or included patients.

Some positive remarks are to be made as well. First, the fact that the patients were treated within the scope of a clinical trial will have guaranteed a certain quality of their treatment as compared to treatment outside clinical trials, as has been

shown before. Second, the authors raise the important issue of insufficient funding for clinical trials, as opposed to funding for basic research, a situation that applies to many European countries. Although this may be changing for small-scale experimental phase I–II studies, e.g. in The Netherlands, financial support from the government for large phase III studies is hard if not impossible to obtain. Without such support, which is clearly needed for the logistics, the statistical support, the data management, and the quality control, medical oncologists are driven into the hands of pharmaceutical industry-driven trials. However, these may not always be designed to answer the most relevant questions we have ourselves and may not always provide us with the most favorable treatment options in terms of healthcare economics. These arguments are in favor of governmental support for clinical research. If governments fail to appreciate this, medical oncologists should organize themselves at a national level to 1) stand united in their request to governments for sufficient funding for independent trials, and 2) install disease-oriented groups that are able to reach consensus on the priority for clinical research questions and to perform large-scale studies which should be very realis-

tic in a large country such as Germany. In several European countries disease-oriented groups are being formed or are already active for common tumor types such as breast, lung, or colorectal cancer. Obviously the EORTC may provide a solid backbone in terms of coordination and logistic support for the initiatives of these national groups.

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References

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