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Editorial

Gold Standard or Wrong Standard?

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Despite the importance of randomized phase III trials, especially to change standard treatment paradigms, the literature shows that critically analyzed, multicenter phase II trials are good predictors of the eventual results of randomized phase III trials, as previously noted in *The New England Journal of Medicine* (*NEJM*).[1–3] Such trials avoid the unintentional bias in patient populations that predictably result in higher response rates and survival rates inherent in single-institution studies that can not be reproduced in multicenter phase II trials or randomized trials. A good example is the results from a single-institution trial of combinations of biochemotherapy in melanoma that could not be reproduced in multicenter phase II trials;[4] this difference was confirmed in randomized phase III trials.[5] Unfortunately, it has become commonplace for expensive, randomized trials to be carried out even when multicenter phase II trials have clearly established the superiority—or lack of superiority—of a new agent compared to standard treatment.

A recent example is the report in the March 13, 2003, issue of *NEJM*, wherein the authors presented the definitive "gold standard," randomized trial of the new selective inhibitor of BCR-ABL tyrosine kinase, imatinib (Gleevec) versus an older standard treatment of cytarabine plus interferon (C/IF) in CML.[6] The results were definitive, prompting the independent data-monitoring board to recommend that these data be "closed." The paper does not say if the trial was interrupted prior to the planned closure date. In terms of complete cytogenetic response (CCR) rate, the superiority of imatinib was obvious with a CCR of 73.8% versus a C/IF of 8.5%. The study allowed a crossover for patients who were not responding to initial therapy. After the crossover, the CCR for imatinib was 39.6% versus 0% for the few patients who crossed over to C/IF. These data suggest that delayed or subsequent imatinib after C/IF is not nearly as efficacious as upfront imatinib.

The molecular remission rats were not described in this paper. The editorial by Peggs and MacKinnon in the same issue states that the complete elimination of BCR-ABL transcripts detectable by polymerase chain-reaction assays was less than 5% with imatinib.[7] The reference is an abstract,[8] making it impossible to compare the patient populations in the two studies. More recently, Hughes et al. published the molecular data in the *NEJM*.[9] Only 47 patients in the C/IF group attained a CCR, whereas 408 patients in the imatinib group experienced a CCR. Importantly, in 377 patients where molecular data were available, those patients gaining at least a 3-log reduction in BCR-ABL transcripts had a negligible risk of disease recurrence over the next 24 months. This degree of "molecular remission"

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occurred in 39% of the imatinib and only 2% of the C/IF patients. The CCR rate was so much higher when imatinib was used first as opposed to after therapy with C/IF, that, in hindsight, one questions whether this randomized trial was necessary. Although the authors say there was "no demonstrable difference in survival between the two groups on an intention to treat basis, and it seems unlikely that any such differences will ever be observed" because of the crossover design, this assertion may be incorrect because so few patients had died at the time of analysis. Given the much higher CCR for the 408 patients who received imatinib initially (73.8%) compared to the 318 patients who received imatinib post-C/IF (39.6%), longer follow-up for deaths may indeed be relevant. Unfortunately, Hughes et al. did not address the difference in molecular remission rates for those who were delayed in receiving the more active agent by being randomized to C/IF.

The authors state that "because of the favorable results of phase II studies of imatinib in late chronic-phase CML, we considered a crossover design to be an essential element of the current study." While this is commendable, the real question is whether this trial was scientifically necessary as well as ethically appropriate. If the survival rate for the patients receiving C/IF who crossed over is inferior to the group that achieved a CCR when given imatinib initially, one might question whether the dramatic results of the phase II studies of imatinib in patients who had already failed similar regimens should have been sufficient for drug approval, making the randomized trial of imatinib versus interferon unnecessary. We submit that the phase II data for imatinib in patients who had failed interferon-based therapy were so compelling that imatinib should have become the new standard therapy without a large randomized trial, just as the activity of rituximab was obvious from phase II trials in relapsed patients with lymphoma.[10] The current scenario is reminiscent of the pentostatin versus interferon randomized trial conducted in hairy-cell leukemia.[11] Even though it was already apparent that pentostatin was less toxic and had a higher response rate in patients who had relapsed or failed to respond to interferon than interferon did as initial therapy, a large randomized trial was conducted that confirmed the superiority of pentostatin.[12] Fortunately, the pentostatin salvage therapy was so effective that there was no overall survival disadvantage for the interferon group. Hopefully, this will be true for imatinib in CML as well.

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