Phase I Clinical Trials in an Era of Increasing Oncologic Success

Although metastatic solid malignancies, particularly in adults, remain a large unmet medical need, there can be little doubt that the recent past has produced a veritable cornucopia of new drugs for the treatment of cancer. In the five years between 2010 and 2014, 37 new molecular entities were approved by the FDA for the treatment of cancer; in the five years between 1995 and 1999, only 20 such agents were approved (information courtesy of CenterWatch). Moreover, many of the newer approvals are targeted agents, either in the form of small molecules or monoclonal antibodies, which avoid many of the unpleasant side-effects associated with non-specific cytotoxic chemotherapy. Oncologists practising today may take for granted the six separate agents currently approved for metastatic melanoma, but it was not that long ago that this disease was associated with a progression-free survival of only six weeks when treated with DTIC, the only available agent at the time.

Despite this incredible progress, many, if not most, patients treated with these newer agents still succumb to their cancers. Malignant cells develop patterns of resistance to targeted agents, and there are still patients who don't respond, for whatever reasons, at all. The search for more effective and safer agents goes on.

Phase I studies are the entry point for the testing of new drugs in humans. For drugs being developed for the treatment of cancer, these trials typically involve patients who have exhausted all established therapies known to provide clinical benefit for their cancers. In the past, this would often mean a patient may have received one, or two prior regimens before being eligible for enrolment into a Phase I clinical trial. For some diseases (like melanoma), a clinical trial often offered at least as good a probability of efficacy as the standard of care, so that it was not uncommon to find previously untreated patients with certain cancers enrolled into Phase I trials. Now, given our new-found success in cancer drug development, potential Phase I patients may have received upwards of five prior regimens, and for certain malignancies, where drugs may be "re-cycled" (i.e., used more than one time in the course of a patient's disease), this number can approach ten prior regimens. This has resulted in a pool of Phase I candidates who have been much more heavily pre-treated than in the past, often have highly-resistant malignancies and a greater burden of metastatic disease, resulting in poor performance scores and poor tolerance of investigational agents and the rigours of an investigational trial. Such patients can easily jeopardise the success of an early-phase trial.

So how should we measure success of a Phase I cancer clinical trial? In the past, the emphasis of such trials was strictly on defining dose-limiting toxicities and the overall adverse event profile of a new agent. The pharmacokinetic properties of the new agent would also have been determined and responses would have been reported, although the expectation of efficacy was low.

The situation, in my view, has changed. Because patients eligible for Phase I studies now may have greater disease burdens, they come into the studies "sicker" than in the past. Many are unable to remain on the study even for the duration of the first treatment cycle due to disease progression, forcing the study sponsor to have to replace subjects. Obtaining pharmacokinetic information is still important, but now there is greater emphasis on translational and pharmacodynamic studies, particularly for targeted agents, often involving tumour biopsies. In patients without superficial metastases, this can involve trying to obtain adequate tissue samples in vital organs, such as the lung or the liver. Venture-backed companies are now under pressure to demonstrate efficacy even in Phase I, or risk a loss of future funding. "Success" in Phase I now often requires the demonstration of efficacy, with proof of mechanism of action in fresh tumour biopsies, in patients with even more resistant tumours than in the past.

Given our success in raising the standard of care in general in the treatment of cancer, all of the stakeholders in cancer drug development need to re-adjust expectations for Phase I studies. Investigators should be more circumspect in who they enroll in such studies – patients with decubitus ulcers probably don't have ECOG performance scores of 1. Sponsors should plan for longer trials to allow for the replacement of subjects who may have to drop out due to rapid disease progression. While Phase I studies with 40 per cent response rates are desirable, this should not be the benchmark of a new drug's ultimate success.

Michael Kurman, M.D is Senior Director of Medical Affairs for INC Research, with 30 years of oncology drug development experience as both a clinical investigator and pharmaceutical executive. Dr Kurman started his career in the practice of oncology, during which he was an investigator on several oncology clinical trials. His background also includes the successful development or launch of four oncology products. His primary interests are in early-phase oncology clinical trial design and drug development, and in strategic portfolio management.
Email: michael.kurman@incresearch.com.