Use of Predictive Markers in Oncology: Are Phase 3 Trials Always Required?

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In this issue of *Oncology*, Kullmann et al. [1] describe an interesting retrospective analysis of the relationship between the presence of a ‘wild-type’ versus ‘mutant’ KRAS and the presence or absence of rash and the outcome of metastatic pancreatic cancer patients treated in a phase 2 trial with cetuximab plus oxaliplatin and gemcitabine. The investigators noted a statistically significant association between the presence of cetuximab-associated rash and superior survival in this patient population. A non-statistically significant favorable impact on survival was also observed in the ‘wild-type’ KRAS subgroup.

This reported experience raises the provocative question of when it is appropriate to utilize in routine (non-trial-based) clinical practice prognostic or predictive biological/clinical marker data generated through either retrospective or prospective studies.

The ‘academic purist’ would likely argue that the results of a prospective phase 3 randomized study which convincingly demonstrates the use of such a marker (e.g. KRAS mutation analysis; development of treatment-associated rash) to modify management favorably impacts a prestudy defined, objectively measurable outcome (e.g. overall survival) should be required before it is appropriate to consider the test acceptable to employ in routine clinical care.

While it is difficult on scientific grounds to disagree with this perspective it is similarly rational to suggest that rigid adherence to this philosophy essentially means that very few biological/clinical markers will ultimately become components of ‘standard-of-care’ cancer management. Further, it is highly likely that this outcome means the abandonment of an unknown number of markers of definite or at least reasonable clinical utility.

Several points can be advanced in support of this conclusion. First, at a minimum such definitive phase 3 trials will require ‘hundreds’ (if not ‘thousands’) of patients and will almost certainly take years to complete and analyze. Second, the studies will unquestionably be very expensive. Finally, it is not an easy task to attempt to name obvious funding sources for such large-scale efforts, particularly considering multiple competing concepts within the clinical research community (e.g. novel ‘targeted’ antineoplastic agents in a particular clinical setting) which will be in superior positions to garner the required financial support (e.g. pharmaceutical/biotech company) for the conduct of any proposed randomized studies.

Should definitive data from randomized phase 3 trials or meta-analyses from multiple such studies always be required before biological/clinical marker data are used in patient care if the ultimate response to this question is that such studies are highly unlikely to be conducted in

most clinical settings? And is this outcome really in the best interests of our patients? Finally, is there an objectively rational and realistically pragmatic alternative approach to the use of such data in the selection of antineoplastic therapy in certain well-defined circumstances?

In an attempt to address these important and complex issues it is the opinion of this commentator that it is reasonable to borrow a concept from the biomedical ethics literature. In a discussion of the validity associated with a physician's decision to offer an individual patient entry into a phase 3 randomized trial many have suggested this is an acceptable clinical practice based on the principle of equipoise [2]. It is argued that if the individual clinician or the community of knowledgeable clinical investigators believes that selection of any one of the specific arms included in a randomized study in a particular clinical setting is a medically acceptable therapeutic alternative for the management of that patient, then it is ethical to advise the individual of the availability of the study or even recommend/suggest participation in the trial. Under these specific circumstances and in the absence of available data in opposition to this conclusion there should be no objectively valid pretherapy reason to believe that the patient's participation in the trial will result in her/his experiencing an unacceptable risk of harm (excessive toxicity or inferior survival).

In the context of the current discussion of the use of biological/clinical makers one would argue that if a number of genuinely acceptable/appropriate therapeutic options are available to be utilized by a treating oncologist in a particular setting then the biological marker may be quite rationally employed to assist in the selection of therapy from among these specific alternative options. Accepting the stated assumption regarding the general equivalence of available management strategies there should be no pretherapy justification for believing any harm will arise that is directly associated with having used this maker to assist in the treatment selection process.

Of crucial importance, this concept absolutely does not imply that a therapy of known benefit in a particular setting, based on the results of a phase 3 randomized trial (e.g. platinum/taxane chemotherapy of advanced ovarian cancer), should be abandoned simply because a biological marker (e.g. in vitro drug sensitivity testing; tumor genetic profile) 'suggests a lack of utility' for that strategy, or conversely that an alternative management approach of unknown benefit in the setting should be used in its place (again, based on the marker results). Examination of these very specific issues would mandate a prospective randomized study designed to address the question of the benefits (or harm) associated with the rejection of standard therapy or the selection of nonstandard therapy in a particular clinical setting.

Assuming that the utility of the development of a skin rash or the presence of 'wild-type' KRAS in pancreatic cancer is confirmed by other investigators, it is rational to argue that employing such testing (or other biomarkers to be explored and reported in the future) may assist treating oncologists in their attempt to design an optimal management strategy to be selected from among equally, but modestly, active antineoplastic approaches in this most difficult clinical setting.

References

- 1 Kullmann F, Hartmann A, Stohr R, Messmann H, Dollinger MM, Trojan J, Fuchs M, Hollerbach S, Harder J, Troppmann M, Kutscheidt A, Endlicher E: KRAS mutation in metastatic pancreatic ductal adenocarcinoma: results of a multicenter phase II study evaluating efficacy of cetuximab plus gemcitabine/oxaliplatin (GEMOX CET) in first-line therapy. *Oncology* 2011;81:3-8.
- 2 Freedman B: Equipoise and the ethics of clinical research. *N Engl J Med* 1987;317:141-145.