Predicting response of molecular targeted therapies: a still possible challenge?

Over the past few years, the development of antitumoral molecular targeted strategies has been replacing the more empiric screening way of research for new cytotoxic drugs. The understanding of the molecular mechanisms which underline carcinogenesis has improved and favored the development of a pattern of targeted drugs that can specifically inhibit cancer pathways and key molecules implicated in different phases of tumor growth and metastases. Despite these efforts, even though some of these new compounds have shown progress, failure rates are still common and impact on survival is modest.

Epidermal growth factor receptor (EGFR) represents an interesting example of a genetically validated target which has partially failed to demonstrate a clinical usefulness for a tailored therapy. Both RNA expression levels and genetic mutations have implicated EGFR as a causal factor in non-small-cell lung cancer (NSCLC), but, despite the presence of EGFR abnormalities in many NSCLC tumors, therapeutic inhibition of EGFR has resulted in significant tumor regression in only 10%–20% of patients. Although some studies have demonstrated the presence of activating EGFR mutations in responsive patients [1], more recent studies have documented response in some patients without apparent genetic alterations in EGFR [2]. In colorectal cancer, as well as in NSCLC, results regarding the role and the magnitude of effect of possible predictive factors is controversial: current selection of patients for cetuximab therapy is on the basis of EGFR expression by immunohistochemistry, but a 25% objective response rate was obtained in a series of colorectal cancers that did not express EGFR by immunohistochemistry, highlighting the potential existence of other predictive markers of response to cetuximab [3]. Moreover, although different authors indicate the importance of EGFR copy number, high disagreement on the magnitude of its predictive effect is present according to different reports. These contrasts underline the tremendous promise and the challenges of using genetic data in target validation. Knowing that a gene is genetically altered is compelling enough to start a preclinical research. In clinical setting, however, research requires appropriate designs for proving the predictive role of markers, which have been well codified. Similarly to the grading of quality of evidence for clinical trials, it is possible to define different levels of quality of evidence for studies on predictive factors. The most appropriate are on the basis of prospective randomized studies powered for detecting interaction between marker levels and treatment as primary or at least secondary end point; studies with the lowest methodological quality derive from retrospective data, using univariate analysis [4]. It is not difficult to note that the majority of studies analyzing predictive marker for EGFR-targeting drugs are on the basis of univariate analysis of retrospective data, without control arm, using surrogate markers of clinical outcomes [5–8]. Moreover, despite the availability of methodological designs for studying predictors of clinical response in phase I, II, and III studies [9–12], the process of clinical drug development rarely considers early testing of predictive factors for selecting responding patients to EGFR inhibitors.

In NSCLC, only post hoc analyses of small subgroups of patients included in phase III studies are available, whereas in colorectal cancer, cetuximab was developed in EGFR ICH-positive patients [13] in phase II trials; however, it was tested on the overall population in phase III without a planned analysis on predictive factors [14]. Developing predictive factors in retrospective uncontrolled series may lead to biased results because of the sample selection and a not standardized evaluation of materials. Furthermore, the introduction of bias by using surrogate instead of clinical outcome is not well recognized: the definition of a cut-off for markers on the basis of the effect on responses can lead to errors similar to the utilization of a suboptimal gold standard for defining the performance of a new diagnostic test. The effect is a reduction of both predictive sensitivity and specificity of the marker. Finally, publication bias may affect the selective publication only of positive studies, increasing the risk of erroneously adopting ineffective markers for patient selection. A more rigorous selection of papers deserving publication in clinical journals, similar to what is implemented for clinical trials reports, has to be warranted.

However, the lack of a good knowledge of predictive factors can be due not only to a bad implementation of methodology. From a technical point of view, reliable predictive tools are needed to apply the appropriate treatments for patients with potentially sensitive tumors only. Difference in criteria for quantifying the presence of markers has to be acknowledged as well as studies for comparison of method have to be implemented. In addition, changes in the mechanism of regulatory approval are needed. According to Chabner [15], sponsors will invest in the research needed to identify subgroups of patients who are likely to have responses only if this process helps them to achieve approval for marketing, giving them a competitive advantage over another product or increasing their market share. For any given indication in oncology, none of these incentives to define the subgroups of...
patients who are likely to have responses may apply: single-agent response rates as low as 10%–15% have been adequate to win Food and Drug Administration approval for indications in oncology for which no other treatments are available. Defining subgroups of patients who are likely to have responses, which could boost response rates in a selected group, may therefore not be necessary for initial approval. On the other hand, from the patient and health service point of view, it is rather important to recognize that development of tumor markers on the basis of bad knowledge of their predictive potential is as harmful as development of bad drugs, both in terms of costs waste and inappropriate choice of drugs for specific patients. Therefore, investigations addressing these issues should be encouraged and ways of funding them should be found, facilitating collaboration between industry- and investigators-initiated trials or providing funding for nonprofit studies. A good example of this effort is offered by the Italian Drug Agency, which economically supports studies aimed at defining predictive factors for molecular target agents. This has prompted the implementation of the ‘TAILOR’ study, a randomized trial in NSCLC, the primary objective of which is to assess the role of K-ras and EGFR expression in selecting patients who can take advantage by using erlotinib. Similar studies are planned for cetuximab in colorectal cancer. These examples are indicating that research of rational selection of drugs on the basis of molecular characteristics is not only needed but also possible.

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