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Editorial Comment

Molecular markers of chemotherapy in advanced colorectal cancer: Back to square one

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The clinical development of fluoropyrimidines in colorectal cancer had a very strong rational basis half a century ago. In fact, colon cancer cells preferentially utilise uracil compared to normal colonic mucosa. Substituting a hydrogen atom with a fluorine atom converted a physiologic metabolite into a lethal poison: 5-FU. This drug almost doubles the median survival of patients with advanced disease compared to best supportive care and produces, approximately, a 10% cure rate when used as an adjuvant in stage III colon cancer. For more than 30 years the field of biochemical pharmacology has elucidated the mechanisms of action and resistance to fluoropyrimidines. New analogues have been designed (5-fluorouridine, 5-fluoro-2-deoxyuridine, capecitabine, ftorafur), and sequential synergistic combinations (methotrexate-5-FU) and modulation by natural cofactors and metabolites (5-FU-leucovorin, 5-FU-uridine, UFT) have been investigated in the hope of improving results. However, these rational developments, so active in preclinical models, produced only marginal results in the clinic.

The next substantial clinical improvement came from the development of oxaliplatin and irinotecan. The huge bulk of data on the pharmacodynamics of the three available agents made it logical to investigate their potential determinants of efficacy or resistance in individual patient's tumours for personalised treatment. The original report by Koopman et al. and the companion review by the same group represent two milestone papers in this field.[1,2] Both papers illustrate the gap between clinical/preclinical correlation studies in this field (almost always 'positive' – sometimes enthusiastic – hardly ever 'negative') and their actual clinical relevance (almost none). The strength of the two publications is undisputable: the original paper reports by far the largest biomarkers/clinical outcome correlations; the comprehensive review (180 papers) takes a very clear and strong stand leading to a straightforward, honest, pragmatic and useful message: no biomarker predictive of chemotherapy efficacy in the advanced setting of colorectal cancer treatment is available today. The Authors never leave the reader with politically correct, but often misleading sentences such as 'the data are promising, however more work is needed…'. They also draw the logical conclusion that the current common practice of conducting retrospective studies on these biomarkers will produce useless results – and they must be commended for this.

The potential reasons for the lack of clinical relevance of biomarkers predictive of chemotherapy efficacy, despite so many reports in the last 20 years, are fully discussed in the two papers and are not repeated here. So should we consider the search for predictors of efficacy as really being back to square one?

Limiting the answer to chemotherapy and the advanced setting of colorectal cancer, then the answer should indeed be yes, in agreement with the Dutch group's strong message (who, by the way, are very careful in restricting their conclu-

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sions to 'chemotherapy in the advanced setting'). However, if we move away from this limited field and look at other areas of colorectal cancer treatment, we do find some hints of optimism, suggesting that improved treatment transits through good translational research. We can recognise two good examples of this. The first regards a predictor of resistance to FU in the adjuvant setting. The solidity and reproducibility of the data on defective mismatch repair (dMMR) indicates that the data does have clinical relevance: dMMR predict for resistance to 5-FU (alone), so that whenever we consider FU single agent for adjuvant therapy of colon cancer, the presence of dMMR contraindicates its use.[3,4] However, we must admit that the contribution of this marker to clinical practice is limited. First, dMMR is present in only 12–14% of cases. Second, the conditions where 5-FU alone is considered the adjuvant therapy of choice are a minority (few stage II high risk patients with advanced age, co-morbidities, etc.).

The relevance of this finding in the adjuvant setting suggests considering a fundamental difference between dMMR and the biochemical parameters investigated by the Dutch group. dMMR is the end result of a series of functions of the cancer cells, whereas the factors considered in the two papers by Koopman et al. refer, in general, to determinants of biochemical reactions. This observation leads to the second example: the clinical relevance of K-RAS as it relates to anti-EGFR antibody therapy.[5,6] K-RAS too reflects a cellular function(s) and not just a biochemical reaction. Unfortunately, even K-RAS is a predictor of resistance when mutated, and only approximately 20% of wild type tumours derive a temporary benefit from the antibodies.

In conclusion, when searching for single biochemical predictors of efficacy of advanced colorectal cancer chemotherapy, we must accept Dr. Koopman's hard conclusion that further retrospective testing of these markers is unlikely to add clinically useful results. However, because the design of prospective studies on the predictive value of biomarkers is so complex and difficult to conduct, we can still pursue the much easier, feasible and faster retrospective correlations, provided the factors investigated are 'pathway limiting factors', rather than just modulators, cofactors or enzymes that are, at best, rate limiting for a single biochemical reaction. The challenge is identifying them.

Conflict of interest statement

None declared.

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