Small Molecule Inhibitors of Tyrosine Kinase: Waiting for the Good News in Colorectal Cancer as Well

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The limited experience (phase I gefitinib plus FOLFOX) reported by Hartmann et al. [1] in this issue of ONKOLOGIE re-proposes a role of small molecule epidermal growth factor receptor (EGFR) inhibitors in the treatment of colorectal cancer. More than 500 antineoplastic agents are in the clinical phase of development: more than the sum of the next two most represented therapeutic classes, anti-infective and digestive system drugs [2]. The constant advances of our understanding of uncontrolled cell proliferation and the other key features of the transformed phenotype will cause this number to grow even further in the near future. These concepts apply to certain tumors more than to others, and one of the most successful fields has been colorectal cancer. There seems to be no plateau in this process of slow but constant improvements in this disease: median progression-free survival (PFS) and overall survival (OS) values in the most promising series are above 10 and 30 months, respectively. This is true to the point that even the most classical endpoints for phase III clinical trials are being challenged in this disease as a result of success [3]. This moderate, but definite success has been the result of true empirics. Actually, the rational drug design of the new biologicals in this disease is somewhat discouraged by 3 factors: the lack of knowledge of the dominant mechanism of action of the new compounds, the lack of preclinical predictive models of efficacy, and the relative success of the empirical approach followed so far in colorectal cancer.

In general the new biologic agents can be classified according to whether they target the cancer cell or its microenvironment. Practical examples of successful targeting of cancer cells are the anti-EGFR antibodies cetuximab or panitumumab, whereas the best example of targeting the microenvironment is bevacizumab. Both are in our current use for the treatment of advanced disease. And their success has also been confirmed by the fact that both have or are about to complete clinical testing in the adjuvant setting of colon cancer.

There is another way of classifying the new biologicals, and this is based upon their chemical structure. Monoclonal antibodies on one hand (the examples reported above) and small molecules on the other. However, one wonders why there are so far no examples of success in this disease with small molecules. These small molecules represent the third generation of compounds derived from the 'tyrphostins' of the eighties [4]. That name was used to identify inhibitors of several cellular tyrosine kinases (TKI) mediating the extremely complex process of signal transduction to the nucleus. Through the years there has been improvement of tyrphostins on two sides: potency (lower and lower K_i) and selectivity of action. The classification of targeting the tumor or the microenvironment applies to these compounds as well, (we have TKI against EGFR or VEGFR) however, the specificity of the target here is less narrow. This may not be so bad. Actually, this may be a plus. In fact, these drugs are enzyme inhibitors and as such they may exert their effects on several targets: considering the clonal evolution of tumors, having an agent that blocks multiple pathways may be better than focusing the activity against a single target [5]. Another potentially favorable feature is that these agents are orally active and in general have half-lives of around 10–24 hours, thus allowing rapid clearance in case surgery is needed.

These new small molecules have had success in a number of solid tumors including GIST, non-small cell lung cancer, renal cancer, hepatocellular carcinoma, pancreatic cancer and breast cancer and in some of these cases the success has been paradigm changing (GIST, renal cell cancer and hepatocellular carcinoma). But so far, no TKI have been approved for the treatment of colorectal cancer, despite the fact that monoclonal antibodies and TKI have been made available for clinical testing at approximately the same time.

The causes of this delay have been twofold: Firstly, lack of substantial efficacy. This pertains to both EGFR TKI and anti-

giogenic TKI. As to EGFR inhibitors, erlotinib and gefitinib, unlike cetuximab and panitumumab, have resulted ineffective as monotherapy [6]. In addition, these agents have failed to provide a clear-cut signal of additional antitumor activity when combined with chemotherapy [7]. Similarly, the multiple kinase inhibitor of the VEGF family, vatalanib, has failed to show additive activity when combined with standard chemotherapy both in first and second line [8, 9].

Secondly, too much added toxicity. It has always been a golden rule of combination chemotherapy not to combine agents with similar spectra of toxicity. This golden rule has become somehow forgotten due to the observation that two agents, such as 5-FU and irinotecan, frequently causing diarrhoea can be rather safely combined in the treatment of colorectal cancer. But now the issue returns: prohibitive diarrhea has been the

major toxicity of the combinations of anti-EGFR agents with standard FOLFOX or FOLFIRI.

Along the line of toxicities, the small molecules present an additional peculiarity: although they generally do not cause the classical severe toxicities of chemotherapy, other toxicities that are low on the objective scales, but hard on the patients, are quite common (asthenia, myalgia, arthralgia, edema, altered taste etc.).

The jury is still out about the role of small molecules in the management of colorectal cancer. The growing number of these compounds and the challenge that drug companies are taking by launching risky, but justified randomized phase III trials on several of these drugs allow a cautious optimism to further enrich our therapeutic armamentarium in this disease.

References

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