Oxaliplatin, colorectal cancer and predictive factors

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The search for predictive factors of response is one of today's greatest challenges in modern oncology. At a time at which the complexity and the cost of treatment are becoming higher and higher, we think it is of great importance to be able to have predictive factors that allow us to avoid unnecessary treatments as well as optimising them for those patients who are sensitive. The approaches to this problem are diverse and involve different groups of drugs and different analysis techniques depending on the specific drug and the goal of the analysis. We have the clearest example in the predictive value of the presence of *kras* mutations in the response to the treatment with anti-EGFR drugs, which together with HERB2 expression in the treatment with trastuzumab constitute the only accepted predictive factors in digestive cancer. Probably, the so-called biologic drugs or therapeutic targets, acting on a very particular aspect of the modes of signal transmission, are sensitive to very specific and concrete markers. The same is not true, however, for the chemotherapy drugs that could be considered "classical", which, on the other hand, continue to be the essential support for colorectal cancer treatment as well as for most tumours. In this field, the analysis of polymorphisms is the most developed in advanced cancer although some other genetic signatures with prognostic value and with possible usefulness in the decision making of adjuvant treatment have been developed. In this volume of Clinical and Translational Oncology, Watanabe et al. introduce us in their article to microarray analysis as a method to obtain a pattern of resistance or sensitivity to oxaliplatin in 40 metastatic patients treated with FOLFOX6 [1]. From the analysis we obtain a genetic signature of 27 genes whose

expression determines the response to treatment with 89.7% of positive predictive value and 100% negative, which equals the *kras* mutation for antiEGFR agents. One of the difficulties in finding sensitive markers is the fact that patients are treated with drug associations that alter the effect that a marker can have on a specific drug. The genetic signature applied to a polychemotherapy scheme can be an advantage in this sense since it analyses it as a whole and not as a concrete point of the cellular metabolism valid for the target agents but probably too concrete for chemotherapy. Although it is possible to establish a pattern of acquired genetic expression resistance to oxaliplatin *in vitro* [2], most studies in the literature analyse specific genes. As the authors mention, the response to oxaliplatin has been significantly related to ERCC1 expression [3, 4], and also to the association of ERCC1 and TS levels [5], although with a predictive value a bit lower than 65–68%. The presence of polymorphisms in these genes modulates their expression and the possibility of being determined in peripheral blood makes its analysis easier. The analysis of polymorphisms in repair genes, especially ERCC1 and XRCC1 associated or not with TS polymorphisms, especially TS 3' URL, achieves significant results [6–8]. In the work by Martinez-Balibrea et al. [9], the united determination of ERCC1 polymorphisms and TS 3' URL allows the separation of two sub-groups of patients treated with FOLFOX or CAPOX obtaining a different response to capecitabine or 5FU combined with oxaliplatin.

There is no comparative prospective study that definitively demonstrates its predictive value. At present though, coming from retrospective analyses, the combined use of polymorphisms TS, ERCC1 and XRCC1 is a useful method to optimise the treatment of patients with metastatic colorectal cancer treated with fluoropyrimidines and oxaliplatin.

The contribution of Watanabe et al. to this work is of great interest regarding the high predictive response rate obtained. The singularity of the study and the small number of patients limits its value and it will be necessary to confirm these hopeful results.

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