Re: Effect of Simvastatin on Cetuximab Resistance in Human Colorectal Cancer With KRAS Mutations

Recently, Lee et al. (1) demonstrated the in vitro and in vivo efficacy of simvastatin in overcoming resistance to cetuximab in a panel of v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutated, but not KRAS wild-type and v-raf marui sarcoma viral oncogene homolog B1 (BRAF)\textsuperscript{V600E} mutated, colorectal cancer (CRC) cells (1). The aim of the work is topical, as KRAS mutation is currently the only biomarker screened in clinical practice to select patients with metastatic CRC for anti–epidermal growth factor receptor (EGFR) therapy and is the major predictive factor of nonresponse to such treatment (2).

The results (1) are intriguing, because they were obtained with a dose of simvastatin equivalent to that used in clinical practice, thereby providing a putative combination of simvastatin plus cetuximab to test in trials for metastatic CRC. Nevertheless, in our opinion, this study has some important limitations. First, the authors genotyped and subsequently divided the colon cancer cell lines used in their study only on the basis of KRAS and BRAF\textsuperscript{V600E} mutations. However, there is compelling evidence that, besides KRAS and BRAF\textsuperscript{V600E} mutations, other mutations in phosphoinositide-3-kinase catalytic alpha polypeptide (PIK3CA) at exon 20 and neuroblastoma RAS viral oncogene homolog (NRAS), along with the loss of phosphatase and tensin homolog (PTEN) expression, are potentially associated with a low response rate to cetuximab (3–6). Although these biomarkers require further validation before their application in clinical practice, a more detailed screening, including analysis of PIK3CA, NRAS and PTEN mutations, would have provided more accurate results to better identify those colon cancer cells responsive to simvastatin plus cetuximab treatment. Such an analysis is all the more necessary as the authors are planning a phase II study in metastatic CRC patients with KRAS mutations. Second, they did not analyze the involvement of EGFR in response to simvastatin. Statins have been reported to interfere with lipid raft formation, which are known to play a critical role in the regulation of EGFR signaling and resistance to anti-EGFR therapy (7). Finally, they stated that simvastatin did not affect the expression of membranous KRAS, but did not specify the values of the densitometric analysis, which would have been helpful to better understand the immunoblotting results. Indeed, simvastatin seems not only to affect KRAS expression, but also to exert an opposite effect on such expression (a decrease in SW403 and an increase in DLD-1 and HT-29 cells). Notably, this was detectable not only comparing KRAS mutant (SW403) with KRAS wild-type (HT-29) cells, but even comparing colon cancer cells harboring the KRAS mutation at two different codons (SW403 and DLD-1). If our observations are correct, the authors should investigate the cause of such discrepancy, as it could represent a confounding factor in data interpretation and introduce a bias in the clinical trial they are planning. Indeed, patients in whom simvastatin increases membranous KRAS expression could have a low response rate despite BRAF inhibition, because of concomitant activation of the AKT pathway. In this context, analysis of PTEN and PIK3CA expression, along with a time course of AKT phosphorylation, makes even more sense to better clarify simvastatin’s mechanism of action. In conclusion, results of Lee et al. (1) are notable, but further studies are needed to select patients who could benefit from this therapy.

GIOVANNI BRANDI
GUIDO BIASCO
SIMONA TAVOLARI

References


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Affiliations of authors: “L. and A. Seràgnoli” Department of Hematology and Oncological Sciences (GBi, GBr) and “Center for Applied Biomedical Research” (C.R.B.A.) (ST), Sant’Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; Interdepartmental Center for Cancer Research (C.I.R.C.) (“G. Prodi”), University of Bologna, Bologna, Italy (GBi); Department of Experimental and Evolutionary Biology, University of Bologna, Bologna, Italy (ST).

Correspondence to: Giovanni Brandi, MD, PhD, “L. and A. Seràgnoli” Department of Hematology and Oncological Sciences, Sant’Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; via Massarenti 9, Bologna 40138, Italy (e-mail: giovanni.brandi@unibo.it).

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