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Precision medicine in chemotherapy: Is there room for advancement in colorectal cancer?

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Genomics-based precision medicine is a cornerstone for the development of tailored oncology treatments. Nowadays, precision medicine is used to choose patients for targeted therapies, monoclonal antibodies, and immunotherapies, which can be used as single treatment or in association with traditional chemotherapy. However, in advanced lines of treatment, single-agent or combinations of chemotherapy agents may be indicated. Unfortunately, genomic biomarkers for chemotherapies are currently lacking. Therefore, treatment indication is untailored, with subsequent poor results in terms of efficacy and survival outcomes.

Recently, van de Haar [1] published results of both a real-world discovery cohort and a retrospective real-world multicenter series of patients treated with single-agent trifluridine/tipiracil (FTD/TPI) in advanced metastatic colorectal cancer (mCRC). A retrospective pooled analysis of the phase III RECOURSE trial was performed, as well [2]. Based on the results of this trial, FTD/TPI is unselectively used as monotherapy for the treatment of all patients with mCRC previously treated with, or are not considered candidates for previously available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-vascular endothelial growth factor (anti-VEGF) agents, and anti-epidermal growth factor receptor (anti-EGFR) agents [2].

All patients included in different cohorts were evaluated for their rat sarcoma (*RAS*) mutational status. Kirsten *RAS* (*KRAS*) codon *G12C* mutation, with a prevalence of 28% in mCRC, was associated with poor survival, and this mutation was correlated with reduced overall survival (OS) benefit of FTD/TPI compared to placebo even in the retrospective pooled analysis of RECOURSE trial. On the contrary, patients harboring *KRAS G13* mutant tumors had significantly improved OS with FTD/TPI *versus* placebo. As a confirmation of these findings, *KRAS G12C* mutation was evaluated *in vitro* in colorectal cancer isogenic cell lines and mCRC-derived organoids. Experiments showed that *KRAS G12C* mutation-driven resistance to FTD was caused by limited FTD-induced DNA damage [1].

Recently, the phase III SUNLIGHT study reported a significant prolongation of OS in mCRC patients treated with FTD/TPI with bevacizumab as compared to patients receiving FTD/TPI, irrespectively of their *KRAS* mutational status [3]. It is possible that bevacizumab may overcome the intrinsic resistance to FTD/TPI given by *KRAS G12C* mutation. To confirm this hypothesis, it would be useful to know codon-specific data on *KRAS* mutations among all patients included in the study in order to allow a post hoc analysis of the link between various *KRAS* alterations and OS associated with the combination treatment [4].

This example is the first proof of genomic-based precision medicine applied to chemotherapy in mCRC. Apart from mCRC, different other primary solid tumors may be treated with exclusive chemotherapy, especially in later lines. For example, FTD/TPI is unselectively indicated in advanced gastric cancer as monotherapy for adult patients with metastatic gastric cancer previously treated with at least two systemic regimens [5].

Starting from the discussed experience, further efforts are needed to identify molecular predictors of response for chemotherapy agents. This would allow the use of personalized treatment even in later lines, avoiding unnecessary therapies and important toxicities in patients evaluated as non-responders.

Abbreviations

FTD/TPI: trifluridine/tipiracil

KRAS: Kirsten rat sarcoma

mCRC: metastatic colorectal cancer

OS: overall survival

RAS: rat sarcoma

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References

1. van de Haar J, Ma X, Ooft SN, van der Helm PW, Hoes LR, Mainardi S, et al. Codon-specific *KRAS* mutations predict survival benefit of trifluridine/tipiracil in metastatic colorectal cancer. Nat Med. 2023;29:605–14.
2. Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, et al.; RECOURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015;372:1909–19.

3. Prager GW, Taieb J, Fakih M, Ciardiello F, Van Cutsem E, Elez E, et al.; SUNLIGHT Investigators. Trifluridine-tipiracil and bevacizumab in refractory metastatic colorectal cancer. N Engl J Med. 2023; 388:1657–67.
4. van de Haar J, Valeri N, Voest EE. Third-line therapy in metastatic colorectal cancer. N Engl J Med. 2023; 389:190–1.
5. Shitara K, Doi T, Dvorkin M, Mansoor W, Arkenau HT, Prokharau A, et al. Trifluridine/tipiracil *versus* placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2018;19:1437–48.