The right chance for temozolomide in metastatic colorectal cancer?

Among big killer cancers, remarkable advances have been achieved in clinical molecular and immunological oncology for a large fraction of patients with lung, breast, or prostate cancer, but only for small subsets of patients with colorectal cancer (CRC)[1]. In the latter histology, the therapeutic armamentarium in the metastatic setting is still based on a chemotherapy backbone with either an anti-VEGF agent without the aid of predictive biomarkers, or an anti-EGFR monoclonal antibody with the aid of *RAS* mutations as negative predictive biomarkers to exclude patients who do not benefit from such treatment. In the salvage setting after failure of previous therapies, the use of the multikinase inhibitor regorafenib or of the novel antimetabolite trifluridine-tipiracil is not driven by predictive biomarkers, and therapy with inhibitors of the immune checkpoint confines its efficacy to MMR deficient tumors. The amplification of *HER2* and rare oncogenic translocations of *ALK*, *ROS1*, or *NTRK1-3* are to be considered emerging targets [1, 2], but these as a whole account for <5% of cases and should be considered pharmacological targets only in *RAS* WT tumors[2], leaving out the substantial fraction (>50%) of *RAS* mutated CRCs as a paramount unmet clinical need.

In this scenario, i.e. the absence of directly actionable molecular alterations in the clear majority of patients, several research efforts have been focused on strategies that exploit the so-called "susceptibility context" of individual CRC tumors. One of these clinical research fields has included the use of alkylating agents such as temozolomide in tumors with a reduced activity of the enzyme O^6-methylguanine-DNA methyltransferase (MGMT) due to epigenetic silencing of the *MGMT* gene[3]. The latter abnormality makes tumors more vulnerable to the specific DNA damage exerted by these drugs. Interestingly, several common *RAS* mutations (associated with G:A transitions) occur more frequently in cancers harboring MGMT deficiency, thus suggesting a role for such therapeutic strategy in this setting [4]. Clinical application of this paradigm has provided

variable results, overall showing objective response rates of 3-16% and progression-free survival of about 2 months with TMZ monotherapy in the advanced setting [5–9]. These data, although sounding promising in the context of the therapeutic landscape of chemorefractory CRC, at the same time can be regarded as disappointing because they have been achieved under the auspices of precision oncology in a totally molecularly selected population. Moreover, data have been provided that in CRC changes in MGMT status can occur over time, making testing on archival tumor samples an unreliable indicator of MGMT at the actual moment of starting treatment with TMZ [6]. Efforts have been made by investigators involved in this clinical research field for further improving molecular selection by considering IHC together with digital PCR quantification of the lack of MGMT activity [10], and application and validation of newer more comprehensive scoring methodologies may lead to more unequivocal evidence of clinical benefit.

All in all, data and consequently guidelines do not support at present time the use of TMZ based on MGMT methylation, and in the current issue of *Annals of Oncology*, the study by Morano et al. [11] capitalizes on their previous results [7, 8, 10] attempting to elaborate a therapeutic strategy that would integrate TMZ in the therapeutic toolbox for mCRC. To this aim, Authors adopted a TEMIRI regimen in which bi-weekly irinotecan has been added to a classic schedule of TMZ based on previous studies in miscellaneous, mainly SNC and pediatric, solid tumors. They chose the chemorefractory setting (≥2 previous lines) and, most importantly, they elected to enroll only patients retaining sensitivity to irinotecan as demonstrated by a documented response or stable disease from the last irinotecan-based regimen and a non-progression under treatment or within 3 months from last administration (i.e. interruption of irinotecan-based therapy for reasons other than progression). Under these circumstances, the primary endpoint of objective response rate (ORR) was established, considering the unsatisfactory 10% of TMZ alone as benchmark, and the study has been declared positive by achieving an ORR of 24% by TEMIRI in this setting.

The interpretation of these data is two-faceted. From a clinical standpoint, Authors must be congratulated for the potential plasticity that this treatment regimen would add to the therapeutic algorithm of mCRC: they propose to opportunistically include in selected patients after 2nd line an original *molecular context of susceptibility-based enhanced chemo re-introduction*. This could adapt to situations where patients come from an irinotecan-based therapeutic break and there is the need of obtaining some more ORR than expected with standard re-introduction or complete change in line of treatment. As a drawback, as admitted by Authors themselves, this strategy can be applied only to the case of treatment holidays or maintenance with adequate irinotecan-free interval, in an overall context that is limited to few patients and supported by a low level of evidence. Finally, the present TEMIRI regimen was quite well tolerated with only 16% patients showing ≥grade 3 adverse events and no treatment-related deaths.

From a molecular and methodological point of view, however, this study does not clarify if and how much the addition of irinotecan truly enhances the antitumor effect of TMZ in this population selected for MGMT deficiency. If on one hand a synergistic effect of the two drugs is hypothesized based on the indirect assumption that topoisomerase II inhibitors may enhance efficacy of TMZ, on the other hand there are no preclinical data in cellular models or PDX provided, and this together with the design of the study - that selects only patients still sensitive to irinotecan - does not allow to discriminate the extent of irinotecan contribution to the observed results and whether a synergistic rather than additive effect does actually take place.

The path of precision oncology in CRC is proving increasingly complex, and the landscape of putative actionable molecular alterations, besides a handful of biomarkers heralding oncogene addiction [1] or mutational load-driven immunotherapy, is giving inconstant results [12, 13]. In this context, all efforts for improving therapeutic results based on molecular biomarkers, especially among *RAS* mutated cancers, should be encouraged. In CRC, methylation of MGMT proved to be a

necessary but not sufficient condition for achieving with TMZ the magnitude of benefit expected by a tailored use of this drug. The current trial of Morano et al., with the boost of irinotecan re-introduction, leveraged this strategy to enhanced results. Whether this might represent a plateau of efficacy will be determined through more preclinical work and further improvement in molecular selection.

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