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BRAF V600E-mutation leads a true change both in diagnosis and within the treatment setting of mCRC

Manuela Maria Campanelli / 7 July 2023

Colorectal cancer (CRC) is a challenging condition for oncologists, who must consistently update their knowledge on the most recent literature outcomes and the latest innovative treatments, as well as consider patients' conditions, desires and resilience to coping with the disease, so as to treat it properly. Oncologists must combine personalised medicine with precision medicine to provide the best quality of life possible for their patients. Although some CRC risk factors can be controlled, by keeping a balance diet, reducing alcohol consumption and increasing physical activity, CRC has indeed a high global incidence across the world, reaching around 1.1 million new cases per year. About 25% of patients are also diagnosed too late, at metastatic stage, and many patients with localised disease go on to develop metastases. However, CRC mortality has declined in Europe since

2012, thanks to screening programmes that have improved the early detection approaches, in addition to the introduction of better therapeutic approaches (A. Cervantes et al., Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up, Annals of Oncology, 34, issue 1, pp. 10-32, January 2023)•

"The median overall survival of metastatic colorectal cancer (mCRC) has also increased over the years, from around 6 months in the 2000s, to 1 year, to the current median of more than 30 months Refractory Metastatic Colorectal Cancer: Current Challenges and Future Prospects – PMC (nih.gov). This is thanks to a deeper knowledge of cancer biology and the identification of key mutations that have allowed the development of targeted therapies to add to traditional chemotherapies in order to define specific standard strategies", says Erika Martinelli, Associate Professor in Medical Oncology, Department of Precision Medicine, Oncology Unit, University of Campania "Luigi Vanvitelli" of Naples.

Patient prognosis is indeed influenced by specific oncogenic drivers that are accumulated in critical genes. It can be affirmed that mCRC is a high heterogeneous disease caused by various genetic alterations that were discovered during the past few decades. The first to be discovered was the oncogene RAS, followed by KRAS and NRAS, which then led to the discovery of RAS/RAF/MEK/ERK (MAPK, mitogen-activated protein kinase) signalling pathway; this was only fully delineated in 1993. From then to now, the pathway has been understood to play a crucial role in how cells sense external stimuli, transferring information from receptors placed in the cellular membranes to the nucleus, and driving both normal and cancer cell proliferation. Belonging to the same intracellular signalling cascade is the B-type RAF kinase (BRAF) oncogene that remained unknown for a long time until it was identified in 2002. Before this date, oncologists only noticed more aggressive progression in some mCRC cases than in others, without knowing why. Today it is well known that BRAF mutations are involved in the development of mCRC, occurring in 8–12% of patients. The most prominent of them being the $BRAF^{V600E}$ mutation, which occurs in 95% of BRAF mutations, and is associated with an aggressive phenotype, a poor prognosis and resistance to standard treatment.

The missing piece of the treatment puzzle

Despite the development of new therapies targeting the involved mutations, nowadays there are still limited data available to determine the best treatment strategies for patients with $BRAF^{V600E}$-mutant mCRC. The international guidelines recommend a doublet or triplet combination chemotherapy plus the vascular endothelial growth factor (VEGF) inhibitor, bevacizumab, based on a small group of patients analysed in the TRIBE studies and retrospective series. In addition, a meta-analysis of five randomised studies found no increased benefits between these two regimens for BRAFV600E-mutant mCRC patients. $BRAF^{V600E}$ is also a predictive marker for limited response to anti-epidermal growth factor receptor (EGFR) antibodies in these patients, and their use in combination with chemotherapy is controversial in the first-line setting. Monotherapies based on the BRAF inhibitors encorafenib, dabrafenib, and vemurafenib, have shown limited treatment effects owing to rapid feedback activation of the MAPK pathway caused by the BRAF inhibition itself. Therefore, an unmet need remains for a more effective treatment for these patients at the beginning of their metastatic cancer journey.

Integrated advice drives oncologists' clinical practice

Nevertheless, the treatment landscape is evolving for these patients and recent insights have changed it greatly over the last two decades. Therefore, organized information about the latest significant and meaningful progress was necessary. The European Society for Medical Oncology (ESMO) Guidelines ESMO guidelines, published in Annals of Oncology in October 2022, described these improvements, and provided new updates on diagnosis and treatment of mCRC and guidance

for the comprehensive management of patients with mCRC. ESMO updated the recommendation of BRAF testing alongside RAS testing for all patients at diagnosis of metastatic disease in order to inform treatment sequence decisions and prevent delays in appropriate treatment.

The ESMO guidelines highlighted the fundamental importance of establishing an initial molecular work-up at the time of diagnosis, to better understand the tumour biology, as well as being useful to establish treatment sequence decisions and understand the prognosis. Oncogenic drivers affect not only the cancerogenesis but also the predictive effect of targeted cancer therapies for mutated signalling pathways. Alongside medical history and physical examination, molecular profiling is becoming essential when choosing the best initial and follow-up treatments.

“All mCRC patients have to be tested at diagnosis for KRAS and NRAS mutations, which are negative predictive factors for the use of anti-epidermal growth factor receptor (EGFR) monoclonal antibodies; for mismatch repair (MMR) and microsatellite instability-high (MSI-H) status to help oncologists identify Lynch syndrome and select patients with MSI-H who can benefit from first-line immunotherapy; and for BRAF mutation status. mCRC patients with the $BRAF^{V600E}$-mutation indeed can receive a specific treatment based on cetuximab-encorafenib, approved in refractory and previously treated cases”, explains Professor Erika Martinelli.

Although BRAF inhibitors are not beneficial as monotherapy in $BRAF^{V600E}$-mutant mCRC patients, they have been shown to be effective when combined with other therapeutic agents, specifically with anti-EGFR monoclonal antibodies such as cetuximab, with or without MEK (mitogenic-activated protein kinase (MAPK) kinase) inhibitors such as binimetinib. This insight comes from the BEACON CRC study, a global, multicentre, randomised, open-label phase 3 trial that compared the triplet regimen of encorafenib, cetuximab and binimetinib with cetuximab and irinotecan-based chemotherapy (control group) and the doublet regimen of encorafenib and cetuximab with control group in 665 previously treated $BRAF^{V600E}$-mutant mCRC patients. The trial resulted in a significant and clinically relevant benefit for both triplet and doublet therapies in terms of objective response rate (26.8% and 19.5%, respectively, vs 1.8% control group, $P<0.0001$), median progression-free survival (4.5 and 4.3 months, respectively, vs 1.5 months in the control group), and median overall survival (9.3 and 9.3 months, respectively, vs 5.9 months in the control group). Since the adverse events observed were slightly higher in the triplet than in the doublet therapy (65.8% and 57.4%, respectively, vs 64.2% in the control group) but the efficacy was similar, the encorafenib and cetuximab regimen was approved for patients with $BRAF^{V600E}$-mutant mCRC who had received prior systemic therapy.

The current ‘state-of-the-art’ therapy for $BRAF^{V600E}$-mutant mCRC management

This novel combination, which allows a paradigm shift in the treatment of $BRAF^{V600E}$-mutant mCRC and a promising reversal of the resistance of this disease to therapy, has raised the question: what is the optimal first-line treatment strategy for $BRAF^{V600E}$-mutant mCRC patients? The answer is not obvious. As the ESMO guidelines have defined specific standard strategies from the second line onwards, there is a lack of clear consensus on therapeutic strategy in the first-line setting. The CAPSTAN study is the first European, retrospective, multicentre and observational trial that tried to assess treatment patterns for $BRAF^{V600E}$-mutant mCRC in routine clinical practice and describe demographic and clinical patient characteristics; it had two objectives: assess the real-world treatment practices for $BRAF^{V600E}$-mutant mCRC and describe demographic and clinical patient characteristics.

The study ran between 1 January 2016 and 31 January 2020; it has provided an interesting snapshot

of real-world mCRC management by evaluating 255 patients with BRAF^{V600E}-mutant unresectable mCRC from seven countries. The study found that most patients received doublet chemotherapy with or without targeted therapy in the first-line setting; FOLFOX (5FU + oxaliplatin) plus bevacizumab and FOLFOXIRI (5FU + oxaliplatin + irinotecan) with/without bevacizumab were the most prescribed regimens (27.1% and 27.1%/19.2%, respectively). “It also highlights the aggressive biology of the BRAF^{V600E} phenotype, as just over half of patients received a second-line therapy and only 30% a third-line therapy. This emphasised the need for establishing the best treatment for this population in a first-line setting, as soon as possible”, says Erika Martinelli. However, the nature of the CAPSTAN study did not allow definitive conclusions about which therapy, whether doublet or triplet chemotherapy, is superior for BRAF^{V600E}-mutant mCRC in the first line. Other studies, such as the TRIBE2 trial and a meta-analysis of five retrospective trials, that compared the two regimens directly, also demonstrated no indisputable benefit of one treatment over the other treatment. That being said, the single-arm phase 2 ANCHOR study evaluated efficacy, safety and quality of life of first-line encorafenib + cetuximab + binimetinib in this specific population. It demonstrated that the triple-targeted regimen is active in untreated BRAF^{V600E}-mutant mCRC patients, reaching an objective response rate of 47.4%, an overall survival of 18.3 months, and a progression-free survival of 5.8 months, and showed a manageable safety profile.

“It is now important to define a specific role of cetuximab-encorafenib, which is a promising first-line therapy as recently demonstrated in clinical trials, although it is still not approved in first-line. Treatments are indeed evolving and some of those that were in experimental stages have now become standard therapies. This could also be the case for cetuximab-encorafenib”, says Erika Martinelli. The Safety Lead In part of the phase 3 BREAKWATER study has already evaluated the tolerability of encorafenib + cetuximab with chemotherapy versus chemotherapy with or without bevacizumab in first- and second-line (Tabernero J et al LBA 26 ESMO 2022). As preliminary anti-tumour activity was seen, the study will evaluate the efficacy of encorafenib + cetuximab in first- and second-line.

Oncologists must combine all the information to build a therapeutic alliance with BRAF^{V600E}-mutant mCRC patients and provide them with an equilibrium between disease and prescribed therapies. A European expert panel consensus was held in 2022, with the aim to help oncologists in their daily commitment and to integrate ESMO guidelines with more clear and useful directions on how to manage these patients in the clinical practice. The expert panel reviewed the most recent scientific data and collected expert opinions to reach an agreement about every step of the journey for patients with BRAF^{V600E} mCRC. Panellists, identified by a coordinating panellist, voted independently and anonymously and provided the recommendation to test ‘at a minimum’ for KRAS/NRAS and BRAF^{V600E} mutations as well as for dMMR/MSI-H status at the diagnosis of metastatic disease, preferring next-generation sequencing. They advised to radiologically monitor BRAF^{V600E}-mutant mCRC patients more frequently than those without BRAF^{V600E} mutations (at least every 2 months) and described four typical scenarios for this population, defining specific therapeutic strategy and sequences for each of them. The experts stated that immune checkpoint inhibitors are the preferred first-line therapy for patients with MSI-H status, and a doublet chemotherapy with or without bevacizumab as first-line therapy for patients with stable microsatellite, reserving the triplet regimen for only selected cases. They confirmed encorafenib + cetuximab as the preferred second-line treatment.

Preferences of each consensus panel member are not always homogeneous when reflecting the heterogeneity of these patients and the complexity of this disease; it demands a patients’ holistic view alongside a deep knowledge of both personalised medicine and precision medicine that must be coordinated and go hand in hand. What might happen if they only matched actionable mutations with targeted drugs, without creating a therapeutic alliance with the patient? Or what might happen

if they only tailored the treatment to patients' needs, without including the targeted drugs profiled on mCRC molecular alterations? Certainly, the outcome would not be optimal for patient management. The new treatments do not rule out the old ones that are still present in today's regimens. 5-fluorouracil, which was the only molecule available when the current oncologists were students, is still a cornerstone of chemotherapy today. Since it is obvious that they cannot treat patients without chemotherapy for the moment, it is important to continue to generate data and carry out studies to improve therapeutic options for $BRAF^{V600E}$-mutant mCRC patients in order to optimise their treatment.