Translational Oncology 14 (2021) 101122

Contents lists available at ScienceDirect

Translational Oncology

journal homepage: www.elsevier.com/locate/tranon

Spotlight

General treatment for metastatic colorectal cancer: From KEYNOTE 177 study

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ARTICLE INFO

Keywords:
Metastatic colorectal cancer
Immunotherapy
MSI-H
BRAF V600E
MSS

ABSTRACT

In the palliative treatment of metastatic colorectal cancer (mCRC), doublet chemotherapy (FOLFOX or FOLFIRI) or triplet chemotherapy (FOLFOXIRI) combined with targeted drugs (cetuximab or bevacizumab) is the main regimen. Recently, microsatellite instability-high (MSI-H) or DNA mismatch repair deficient (dMMR) was discovered as a biomarker to distinguish immunotherapy-benefited populations. In this context, recently published randomized phase III clinical trials tested the efficacy and safety of immunotherapy and traditional chemotherapy with or without targeted drugs as first-line treatment for patients with MSI-H/dMMR mCRC.

Here, we briefly analyze this article and further discuss immune monotherapy or double immunotherapy for patients with MSI-H/dMMR mCRC, the immunotherapy for patients with *BRAF V600E* mutant mCRC, and the immunotherapy for patients with microsatellite stable mCRC.

Evidence suggests that about 4% - 5% of patients with metastatic colorectal cancer (mCRC) are with microsatellite instability-high (MSI-H)/DNA mismatch repair deficient (dMMR). The clinical efficacy and safety of immunotherapy (pembrolizumab monotherapy or nivolumab monotherapy) in the late-line treatment for patients with MSI-H/dMMR mCRC was proved in several clinical trials [1,2]. The door to immunotherapy for mCRC was opened from then on. As the efficacy of immunotherapy in the late-line treatment was a satisfaction, the efficacy of it in the first-line treatment inevitably aroused clinicians' and scientists' curiosity. In 2020, immunotherapy of mCRC ushered in a bumper harvest, and the question was answered. The position of immunotherapy anti-programmed death-1 (PD-1) antibody in the first-line treatment of patients with MSI-H/dMMR mCRC was established by Keynote 177 study.

Keynote 177 study was a phase III study, the open-label clinical trial enrolled 307 patients with MSI-H/dMMR mCRC who had not previously received treatment, to receive pembrolizumab or chemotherapy (5-fluorouracil-based therapy with or without bevacizumab or cetuximab). The two primary endpoints were progression-free survival (PFS) and overall survival (OS). After a median follow-up of 32.4 months, pembrolizumab was superior to chemotherapy with respect to PFS (median, 16.5 vs 8.2 months; hazard ratio, 0.60; 95% confidence interval [CI], 0.45 to 0.80; $P = 0.0002$), overall response rate (ORR) (43.8% vs 33.1%; $P = 0.0275$), and median duration of response (not reached vs 10.6 months). Pembrolizumab achieved PFS and ORR superiority over standard chemotherapy with a lower incidence of grade ≥3 treatment-related adverse events (22% vs 66%) [3]. Moreover, the latest data updated at the American Society of Clinical Oncology (ASCO) annual meeting in 2021 showed that pembrolizumab significantly prolonged PFS2(Time from randomization to second-line treatment's disease progression or death) when compared with the chemotherapy group (median, not reach vs 23.5 months; hazard ratio, 0.63). Based on this landmark study, pembrolizumab was approved by the National Comprehensive Cancer Network (NCCN) guideline as the first-line treatment in patients with MSI-H/dMMR mCRC and has been updated in version 2021 of the Chinese Society of Clinical Oncology guideline for Colorectal Cancer.

In this study, it can be found that in the chemotherapy group, the median PFS was 8.2 months (range: 6.1–10.2 months) and the ORR was 33.1%, which suggest that the response of patients with MSI-H/dMMR mCRC to standard chemotherapy was poor but relatively consistent. In pembrolizumab group, a median PFS of 16.5 months was achieved, but the PFS ranged from 5.4 to 32.4 months with an absolute difference of 27.0 months. The ORR was only 43.8% but the progressive disease (PD) rate was 29%. Regarding the relatively low response rate with im-

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https://doi.org/10.1016/j.tranon.2021.101122
Received 20 March 2021; Received in revised form 7 May 2021; Accepted 7 May 2021

munotherapy, we could notice that the PFS curve appeared crossover before 6 months, which suggest that the immunotherapy might respond slower. Combined with the fact that the PD rate of pembrolizumab group was significantly higher than that of the chemotherapy group (29.4% vs 12.3%), which also indicate that some patients might be resistant to anti-PD-1 antibody. Another reason is that whether a patient was MSI-H/dMMR was determined by the research center, while there are certain differences in the identification between immunohistochemistry and fluorescence in situ hybridization, thus patients who were not truly with MSI-H/dMMR might be enrolled as well. Moreover, the study performed the response evaluation by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 rather than modified RECIST 1.1 for immune-based therapeutics (iRECIST), which might impact the response evaluation and lead to a part of the pseudoprogression. Also, the subgroup analysis showed that patients with *KRAS/NRAS* mutation could not benefit from pembrolizumab. Thus, even patients with MSI-H/dMMR mCRC still could respond differently to immunotherapy. MSI-H/dMMR is a satisfaction but not the only biomarker, more potential biomarkers are still needed to screen for the dominant population and perform more accurate stratification.

There are three aspects related to this trial worth looking at:

Immunotherapy for MSI-H/dMMR mCRC: immune monotherapy or double immunotherapy

The CheckMate-142 study enrolled 45 patients with MSI-H/dMMR mCRC who received nivolumab plus low-dose ipilimumab as first-line treatment. The latest result, updated at ASCO annual meeting in 2020, showed that the ORR was 69% (6 cases are complete response), and the median PFS was not reached. The PFS and OS rates at 24 months were 74% and 79%, respectively, which were superior to the monotherapy data of the Keynote 177 study [4]. Moreover, the subgroup analysis of *KRAS* status showed that if given nivolumab combined with ipilimumab, the response rate of patients with *KRAS* mutation and *KRAS* wild-type were 57% and 55% ($P = 0.99$), respectively. We may conclude that for patients with MSI-H/dMMR mCRC, both *KRAS* wild-type and *KRAS* mutant patients could derive benefit from double immunotherapy in first-line treatment. Considering that it was a single-arm study with small sample size, further studies are still needed in the future to clarify it.

Immunotherapy for patients with *BRAF V600E* mutant mCRC

About 7% of patients with CRC carry *BRAF V600E* mutation, 21% of them also exhibit MSI-H/dMMR phenotype. Among *BRAF* mutations, only *BRAF V600E* mutation contributes to the poor prognosis. As conventional chemotherapy combined with the anti-epidermal growth factor receptor (EGFR) drug could not benefit patients with *BRAF V600E* mutant mCRC on PFS and OS, researchers began to explore the feasibility of other therapies. The subgroup analysis of *BRAF V600E* mutation in the Keynote 177 study showed that for patients with MSI-H/dMMR mCRC, the clinical benefit could be obtained from pembrolizumab monotherapy regardless of *BRAF V600E* mutation. Moreover, the subgroup analysis of SWOG 1406 study and BEACON study showed that patients with *BRAF V600E* mutant and MSI-H/dMMR mCRC responded poorly to the VIC regimen (anti-EGFR antibody and BRAF inhibitor combined with irinotecan) and doublet combination (anti-EGFR antibody +BRAF inhibitor)/triplet combination (anti-EGFR antibody +BRAF inhibitor +MEK inhibitor) [5,6]. Therefore, for patients with mCRC having MSI-H/dMMR and *BRAF V600E* mutation, the anti-PD-1 antibody still should be the first choice.

Immunotherapy of MSS mCRC

Up to 95% of patients with mCRC are microsatellite stable (MSS), but the efficacy of immunotherapy is far less than that of the patients with MSI-H/dMMR. Based on existing research data, there are two main approaches to solve this crucial clinical problem. First, select potential beneficiaries of immunotherapy through other biomarkers such as high tumor mutation load or POLE gene mutation. Second, explore new combination therapies such as immunotherapy combined with anti-angiogenesis agents, anti-EGFR drugs, or chemotherapy.

Since 2019, the REGONIVO study set off a wave of late-line immunotherapy for patients with MSS mCRC, which enrolled patients with MSS mCRC and assigned them to receive regorafenib plus nivolumab, the 33% of ORR was reached (updated at ASCO annual meeting in 2020) [7]. Several other clinical studies such as the REGOTOR study of toripalimab combined with regorafenib and the LEAP-005 study of pembrolizumab combined with lenvatinib also showed the application prospect of anti-PD-1/PD-L1 antibody combined with anti-angiogenesis agents in patients with MSS mCRC.

A phase II CAVE study enrolled patients with mCRC having *RAS* wild-type/MSS and treated them with avelumab plus cetuximab as a rechallenge strategy. The results, which were released in the European Society for Medical Oncology (ESMO) annual meeting 2020, showed an ORR of 7% and a disease control rate (DCR) of 65% [8].

Besides, in the Keynote 651 study (updated at ESMO annual meeting in 2020), pembrolizumab combined with modified FOLFOX7 as first-line treatment for patients with MSS mCRC achieved an ORR of 59% and a DCR of 94%. Pembrolizumab combined with doublet chemotherapy as second-line treatment for patients with MSS mCRC achieved an ORR of 15% and a DCR of 63% [9].

Precision medicine brings more new therapeutic strategies, drug discovery and development and gene-oriented treatment. Clinicians are responsible to make individualized and comprehensive evaluations of patients and choose the best treatment after assessment of the advantages and disadvantages.

Author contribution

Yuwei Ding and Shanshan Weng wrote the original draft. Xinyu Li, Ding Zhang, and Adilai Aisa performed literature searching. Ying Yuan critically revised the paper. All authors read and approved the final manuscript.

Funding

This work was supported by National Key R&D Program of China (2018YFC1312100 and 2017YFC0908200) and Natural Science Foundation of China (81872481 and 81902956).

Declaration of Competing Interest

The authors report no potential conflicts of interest.

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