Editorial

Mismatch repair deficiency in rectal cancer: an evolving scenario

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Comment on: Wu Z, Hu H, Wang C, *et al.* The prognostic and predictive value of mismatch repair status in patients with locally advanced rectal cancer following neoadjuvant therapy. Ann Transl Med 2022;10:491.

Submitted Jul 08, 2022. Accepted for publication Aug 27, 2022.
doi: 10.21037/atm-22-3529
View this article at: https://dx.doi.org/10.21037/atm-22-3529

A decade ago, the Cancer Genome Atlas Network carried out a comprehensive molecular characterization for colorectal cancer patients. The hypermutated subtype was defined in 16% of them, most with high microsatellite instability (MSI-H) associated with hypermethylation and *MLH1* gene silencing. Moreover, one quarter of these hypermutated tumours had somatic mutations in the DNA mismatch repair (MMR) genes including *MLH1*, *MLH3*, *MSH2*, *MSH3*, *MSH6* and *PMS2*; or in the *POLE* gene. Additionally, hypermutated tumours were more common in the right side of the colon, had a higher proportion of *BRAF* mutations, and some classical mutations in genes like *APC* or *TP53* were less frequent than in non-hypermutated tumours (1). A few years later, the consensus molecular subtypes of colorectal cancer were reported by Guinney *et al.* This consensus defined a CMS1 subtype as an MSI immune tumour which was present in 14% of the patients. Characteristics of CMS1 tumours were as follows: hypermutated status with MSI-H and defective MMR, low prevalence of somatic copy number alterations, high frequency of *BRAF* mutations, diffuse immune infiltrate, strong activation of immune evasion pathways, frequently diagnosed in females, high proportion of right-sided lesions, higher histopathological grade, and poor survival after relapse (2).

Despite the previous evidence, non-metastatic colorectal cancer treatment has been unaltered, and surgery is the only curative approach for these patients. Although the best regimen has not been yet stablished, the standard therapeutic approach for stage II and III rectal cancer consists in a multimodal treatment with chemotherapy, radiation, and surgery. Neoadjuvant chemoradiation improves local control (6% local recurrence at 5 years) and toxicity (27% of grade 3 to 4 adverse events) when compared to its adjuvant administration, but without any beneficial impact in survival (76% alive at 5 years) (3). Total neoadjuvant therapy with the administration of neoadjuvant chemotherapy plus chemoradiation is a trending strategy for localized rectal cancer. In a recent meta-analysis, total neoadjuvant treatment had a significant higher complete pathological response (22.3% *vs.* 14.2%; P<0.001), a better 3-year disease-free survival (70.6% *vs.* 65.3%; P<0.001) and a higher 3-year overall survival (84.9% *vs.* 82.3%; P=0.006) (4). However, due to the late complications and the toxic effects of the multimodal treatment approach (anorectal dysfunction, sexual dysfunction, bone fractures, etc.), new treatment approaches are being explored, particularly in patients with potential biomarkers predicting response for novel treatments.

The article published by Wu *et al.* presents us a large retrospective cohort of localized rectal cancer in which the authors explored the predictive value of MMR deficient status after neoadjuvant treatment either with chemoradiotherapy or chemotherapy alone. Among the 854 stage II and III rectal cancers included, only 7.4% were MMR deficient by immunohistochemistry of MLH1, MSH2, MSH6 and PMS2 proteins. It reflects that MMR defective tumours are more frequent in right-sided tumours, but the proportion in rectal cancer is still significative. Accordingly with previous reports, MMR defective patients were younger and have more mucinous histopathology compared to MMR proficient tumours. After neoadjuvant treatment, MMR deficient patients had a significant lower tumour regression grading (TRG 0/1) compared with MMR proficient tumours (28.6% *vs.* 43.7%; P=0.027) but no differences were observed in ypStage or complete pathological response (15.0% *vs.* 12.9%), respectively.

Neoadjuvant chemotherapy alone had a similar outcome with a significant lower TRG 0/1 (9.1% *vs.* 30.3%; P=0.013) but without any difference in complete pathological response (6.1% in both groups). Chemoradiation therapy achieved similar TRG 0/1 (50% *vs.* 64.2%) and complete pathological response (26.7% *vs.* 22.5%) between MMR deficient and proficient tumours. MMR deficient status was associated with a significant lower disease-free survival [hazard ratio (HR) =0.38; P=0.013], especially for ypStage II/III patients, with similar results in local recurrence-free survival. Unexpectedly, the authors did not find any significant differences in survival between MMR deficient and proficient tumours when they performed a separate analysis for chemoradiation therapy and chemotherapy alone neoadjuvant treatment (5).

This potential lack of benefit in terms of TRG with the standard treatment for MMR deficient local rectal cancer may be implemented by introducing immunotherapy agents into the armamentarium. One of the most powerful predictive factors for clinical benefit with checkpoint inhibitors treatment is MMR deficient cancer, including local rectal cancer. Pembrolizumab, a monoclonal antibody against PD-1 receptor, has the agnostic indication by the FDA for MMR defective cancer patients and EMA indication is under evaluation (6). In second-line MMR defective advanced colorectal cancer, pembrolizumab had shown encouraging results with 40% of objective response rate and median survival not reached (7). The combination anti-PD-1 and anti-CTLA-4 monoclonal antibodies has also shown impressive results in MMR deficient colorectal cancer refractory to previous lines of treatment. The CheckMate-142 trial studied the combination of nivolumab and ipilimumab in this setting, showing 31% of objective response rate and 69% of disease control rate, with median duration of response not reached after a median follow-up of 12 months. This outcome is hard to obtain with the actual available therapies in the third line of colorectal cancer (8). Finally, immunotherapy has already moved to the first-line treatment for MMR defective advanced colorectal cancer. The KEYNOTE-177 trial demonstrated that pembrolizumab treatment was superior to chemotherapy in progression-free survival (16.5 *vs.* 8.2 months; HR =0.6; P=0.0002) and objective response rate (44% *vs.* 33%), with a non-significant benefit in overall survival (median survival not reached with pembrolizumab *vs.* 36.7 months; HR =0.74; P=0.036) in the first-line of MMR defective metastatic colorectal cancer, due to the use of pembrolizumab in second-line treatment in 60% of the patients. Moreover, first-line pembrolizumab was associated to fewer treatment-related adverse events in the trial compared with chemotherapy treated patients (9,10).

Focusing on the treatment of localized colorectal cancer and very recently, Verschoor *et al.* communicated the final efficacy analyses of the NICHE study at the ASCO 2022 meeting. In this trial, 63 non-metastatic colon cancers were treated with a combination of immunotherapy (ipilimumab 1 mg/kg for 1 dose plus nivolumab 3 mg/kg for 2 doses) and programmed surgery within 6 weeks after; 32 of the patients were MMR defective and the remaining 31 patients were MMR proficient. As previously mentioned, MMR defective patients were younger, with higher T and N stage, and primary tumours were located more frequently in the right side of the colon. Among the MMR deficient patients, all patients achieved a pathological response, 69% of them with a complete pathological response. MMR proficient patients also benefited from neoadjuvant immunotherapy with 29% pathological responses and 13% complete responses. After more than 2 years of follow-up, none of the MMR deficient patients have recurred and two patients (6%) of the MMR proficient patients group relapsed, both non-responders (11). Furthermore, neoadjuvant PD-1 blockade with dostarlimab has shown impressive results in a phase II trial with MMR deficient local rectal cancer patients. Consistently with previous studies, a high proportion of patients were female, diagnosed at a younger age and with an advanced stage (75% with T3-4 tumours and 94% were node positive). The first 12 patients that received the scheduled 6 months of dostarlimab treatment, experienced a clinical complete response after evaluation with rectal magnetic resonance imaging, endoscopy, and physical examination. No chemoradiotherapy or surgery was administered according with the study protocol and no patients have had disease progression after a median follow-up of 12 months. Larger studies are warranted to demonstrate the benefit of this approach (12).

The article by Wu *et al.* concludes relevant information from a retrospective cohort study of the benefit of the actual treatment of local rectal cancer, focusing on the effect of defective MMR carriers. The actual scenario for these patients is moving towards the upfront use of immunotherapy agents. The evidence of checkpoint inhibitors efficacy in MMR defective advanced colorectal cancer is clear after the positive results of the phase III trial (9). By the time being, the information of immunotherapy treatment for localized colorectal cancer is scarce but encouraging. Neoadjuvant immunotherapy may have the potential to become the standard of care for a defined group of colorectal cancer patients. A randomized trial to compare upfront immunotherapy with the standard treatment in MMR defective local rectal cancer

is quite unfeasible due to the low proportion of cases and ethical issues. Nevertheless, Wu's and other study results are useful as a baseline information, to know the benefit of upfront immunotherapy, and also, to draw conclusions in the absence of a randomized trial.

Acknowledgments

We thank to our cancer patients and their families.
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3529/coif). FL received support for attending meetings and/or travel from BMS and MSD. FL is an advisory board for BMS and MSD. AC received travel and congress registration from MSD, BMS. AC is a member of Independent Data Advisory Committee for Hutchinson Pharma. AC is an advisory board for Mylan - Viatris, Baxter, Daiichi-Sankyo. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Longo F, Carrato A. Mismatch repair deficiency in rectal cancer: an evolving scenario. Ann Transl Med 2022;10(18):951. doi: 10.21037/atm-22-3529

