Immune checkpoint therapy in colorectal cancer: is first better than last?

Yui Kaneko1, Zainab Naseem1, Neil Strugnell1, Frances Barnett2, Basil D’Souza1, Ankur Sidhu1, Andrew Bui1,3, Toan Pham1,4

1Division of General Surgery, Colorectal Unit, Northern Hospital Epping, Melbourne, VIC, Australia
2Division of Medical Oncology, Northern Hospital Epping, Melbourne, VIC, Australia
3Division of General Surgery, Colorectal Unit, Austin Hospital, Melbourne, VIC, Australia
4Division of Surgery, Colorectal Unit, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Immunotherapy advances involving checkpoint inhibitors have revolutionized treatment for various cancers. In colorectal cancer (CRC), the application of immune checkpoint inhibitors (ICIs) is well-established for metastatic or unresectable microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) disease. However, the role of ICIs in the neoadjuvant setting has yet to be determined. The question remains: can neoadjuvant immunotherapy alter the management of MSI-H/dMMR CRCs in the future?

Let us first summarize how MSI-H/dMMR CRC is well-suited for ICI therapy. The dMMR CRC cells typically have higher mutational burdens than their mismatch repair-proficient (pMMR) counterparts [1]. This results in more non-self-proteins being produced and displayed on the cell surface, making them more likely to be recognized by the body’s immune system as foreign or a so-called hot cancer. Consequently, a cytotoxic response is triggered to eliminate these cells. Unfortunately, cancer evolution has enabled malignant cells to exploit a fail-safe signal employed by healthy cells to subdue aberrant autoimmune attacks by upregulating inhibitory ligands for 2 immune checkpoint receptors (ICRs)—programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)—found on immune cells. As a result, when a cytotoxic lymphocyte attempts to destroy these cancer cells, it is inhibited. The groundbreaking discovery of these ligands was acknowledged when the 2018 Nobel Prize in Physiology or Medicine was awarded to Professors Tasuku Honjo and James Allison for their work on PD-1 and CTLA-4, respectively [2].

ICI therapy with pembrolizumab is currently approved for metastatic MSI-H/dMMR CRC. The pivotal study leading to this indication was the KEYNOTE-177 trial [3], which demonstrated that pembrolizumab was associated with a superior overall response rate compared to standard chemotherapy (43.8% vs. 33.1%) in metastatic MSI-H/dMMR CRC. In the final analysis, the superiority of pembrolizumab over chemotherapy for overall survival was not demonstrated. However, at a median follow-up of 44.5 months, a trend was observed towards improved survival, with median overall survival not reached with pembrolizumab treatment versus 36.7 months with chemotherapy (hazard ratio, 0.74; 95% confidence interval, 0.53–1.03; P = 0.036) [4]. Importantly, the pembrolizumab group experienced fewer serious treatment-related adverse events than the chemotherapy group [4]. That study supports pembrolizumab as an effective therapy for patients with metastatic MSI-H/dMMR CRC.

In 2017, the US Food and Drug Administration (FDA) approved pembrolizumab for the treatment of patients with unre-
sectable or metastatic MSI-H or dMMR solid tumors, including CRCs, that had progressed after chemotherapy treatment. The following year, the FDA approved nivolumab, either alone or in combination with ipilimumab, for patients with MSI-H/dMMR that progresses after standard chemotherapy [5].

Recent studies of stage III melanoma have demonstrated promising results for ICIs in the neoadjuvant setting relative to adjuvant therapy [6, 7]. The neoadjuvant administration of immunotherapy offers a window of opportunity to elicit a stronger and broader tumor-specific T-cell response than would be expected in the adjuvant setting. Furthermore, importantly, ICIs are most effective when a demonstrable antigen load is present, as with metastatic disease or when administered in a neoadjuvant setting with cancer in situ [7, 8]. Neoadjuvant immunotherapy also has been and/or is currently being evaluated in the contexts of many other cancers, including CRC, with promising clinical trial data available. In the NICHE trial [8], researchers assessed the efficacy of neoadjuvant immunotherapy in pMMR and dMMR stage I to III colon cancer. Initial results were encouraging, with neoadjuvant treatment of early-stage colon cancer using a single dose of ipilimumab and 2 doses of nivolumab achieving degrees of pathological response in all dMMR tumors (including pathologic complete response in 12 of 20 cases) and in 4 of 15 pMMR tumors. The immunotherapy was well tolerated, with only 13% of patients experiencing grade 3 to 4 immune-related toxicities, and importantly, it did not compromise planned surgery in any patient. The NICHE-2 study group further investigated dMMR colon cancer; preliminary results validated their previous trial, with a major pathologic response rate (defined as < 10% residual tumor) of 95% and a complete pathological response rate of 67% [9].

Similarly, the PICC (PD-1 Inhibitor in Microsatellite Instability Colorectal Cancer) trial [10] was a single-center randomized clinical trial conducted in China, in which 34 patients with MSI-H/dMMR locally advanced colorectal cancer received neoadjuvant toripalimab, either alone or in combination with celecoxib, prior to surgical resection. The preliminary results showed high pathological complete response rates of 88% in the toripalimab plus celecoxib group and 65% in the toripalimab monotherapy group, which is consistent with the results of the NICHE-1 and NICHE-2 trials. Additionally, 2 clinical trials have demonstrated complete response from neoadjuvant immunotherapy [11, 12]. A retrospective multicenter study in China [11] included 73 patients with localized dMMR CRC who received PD-1 inhibitors as neoadjuvant therapy. Of these patients, 23 did not proceed to surgery, and 17 of these experienced a complete radiological response. The reported 2-year tumor-specific disease-free survival and overall survival rates were both 100%. The other trial was a prospective phase 2 study conducted at the Memorial Sloan Kettering Cancer Center (New York, NY, USA) [12], in which single-agent dostarlimab was administered as neoadjuvant therapy in cases of dMMR stage II or III rectal adenocarcinoma. A total of 12 patients completed treatment with dostarlimab monotherapy, achieving a 100% clinical complete response and no evidence of recurrence after at least 6 months of follow-up without chemoradiation or surgery. No significant adverse events were reported.

Neoadjuvant immunotherapy is a rapidly developing area in the treatment of MSI-H/dMMR CRC. A substantial proportion of these patients have Lynch syndrome; as such, they tend to be younger, meaning that preservation of fertility, sexual function, and bowel function is particularly important. If immunotherapy is shown to have long-term efficacy and safety, it may be possible to avoid the traditional therapeutic modalities for rectal cancer of surgery, chemotherapy, and radiotherapy, potentially leading to a significantly improved quality of life compared to current treatments [13]. From a practical standpoint, MMR status testing must be routinely requested on preoperative biopsies from patients with newly diagnosed CRC.

Now is an opportune time to establish additional clinical trials to validate the findings of international studies, assess local feasibility, identify the most effective treatment and duration, and correlate the pathological response with disease-free and overall survivals. The current data are promising, suggesting that neoadjuvant immunotherapy could become the first-line therapy or standard of care in MSI-H/dMMR CRC. However, the existing evidence relies on preliminary findings from limited clinical trials, due to the relatively low prevalence of MSI-H/dMMR among CRC cases. Hence, more research is required to validate long-term efficacy and safety in this patient population.

ARTICLE INFORMATION

Conflict of interest
No potential conflict of interest relevant to this article was reported.

Funding
None.

Author contributions
Conceptualization: all authors; Writing–original draft: YK, Writing–review & editing: all authors. All authors read and approved the final manuscript. All authors contributed to the work and read and approved the final manuscript.

https://doi.org/10.3393/ac.2023.00248.0035
REFERENCES

6. van Akkooi AC, Blank C, Eggermont AM. Neo-adjuvant immunotherapy emerges as best medical practice, and will be the new standard of care for macroscopic stage III melanoma. Eur J Cancer 2023;182:38–42.