Kong Joseph (Orcid ID: 0000-0002-1392-2480)
Heriot Alexander (Orcid ID: 0000-0001-9846-8776)

Title: Shifting the treatment paradigm for patients with mismatch repair deficient colon cancer – is there a role for immunotherapy?

Joseph C. Kong, MBChB, FRACS, MS, PhD,[1-3] Michael Flood, MBBCh BAO, MRCSI,[1-3] Robert G. Ramsay, PhD,[2-3] Satish K. Warrier, MBBS, FRACS, MS[1-3] Alexander Heriot, FRACS, MD,[1-3]

[1] Division of Cancer Surgery, [2] Division of Cancer Research, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

[3] Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Victoria, Australia

Correspondence: Dr Joseph Cherng Kong, Division of Cancer Surgery, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, Victoria, 3000, Australia, e-mail: joekong@gmail.com

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An estimated 15% of all colorectal cancers are attributed to deficient mismatch repair (dMMR), underpinned by defective DNA mismatch repair. Of these, 3% are associated with Lynch syndrome, whereas the other 12% are sporadic, resulting from an acquired hypermethylation of *MLH1* gene.[1] Common clinical features associated with dMMR colorectal cancers include the propensity to arise in the proximal colon, an abundant lymphocytic infiltration, and a mucinous and/or signet ring cell morphology.

Although these patients have a slightly better prognosis when compared by stage to proficient mismatch repair (pMMR) colorectal cancers, dMMR tumours do not respond as effectively to the conventional fluorouracil-based chemotherapy.[2] Particularly in the metastatic setting, a combined multimodality strategy is usually employed. This often involves administering 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) with specific molecular target inhibitors such as those binding to the vascular endothelial growth factor A (bevacizumab)[3] and the epidermal growth factor receptor (cetuximab).[4] However, in light of the recent advances in immunotherapy and the understanding of the immune architecture of the tumour microenvironment, another therapeutic option for dMMR colorectal cancer has evolved.[5]

Immune cells, such as cytotoxic T-cells play a key role in tumour suppression. Unfortunately, colorectal cancer has the ability to evade these cytotoxic T-cells through a number of specific checkpoint molecules, such as PD-1, PD-L1, PD-L2 and CTLA-4. Immunotherapy can block these checkpoint molecules, allowing the cytotoxic T-cells to be re-invigorated and affording successful cancer-cell killing. The relatively high lymphocytic infiltrate characteristic of dMMR colorectal cancer has further encouraged testing of this hypothesis. In a phase II clinical trial by Le et al., a durable objective tumour response to the PD-1 inhibitor, pembrolizumab,

was shown in four out of ten dMMR treatment-refractory metastatic colorectal cancers.[5] This was further validated in the Checkmate 142 trial, which assessed another PD-1 inhibitor, nivolumab. After a median follow-up of 12 months, the objective response was 31.1% (23 of 74 patients), with 34.8% of patients remaining progression-free at 12 months.[6]

This treatment paradigm has since shifted towards the neoadjuvant setting for dMMR non-metastatic colorectal cancer. In the phase II NICHE trial, forty patients with dMMR or pMMR stage I-III colon cancer were selected to receive a single dose of ipilimumab (CTLA-4 inhibitor) and two doses of nivolumab with a six-week interval to definitive surgery. The most astounding findings were that all twenty dMMR patients had some degree of response to neoadjuvant immunotherapy. Nineteen patients had what was considered a major pathological response (<10% viable tumour identified), of which twelve (60%) were deemed complete (pCR). As for the pMMR colon cancers, 4 of 15 showed a pathological response, three major responses and one partial response.[7] Interestingly, the phase III FOXTROT trial, which assessed neoadjuvant chemotherapy in locally advanced colon cancer, 95% of dMMR patients (n=106) showed little or no pathological response. [8] This further emphasises the impressive pCR reported by the NICHE study. In addition, FOXTROT, which is yet to be formally published, is the first trial to show that pathological response to neoadjuvant therapy in colon cancer is associated with the risk of recurrence. In this vein, one can hypothesise that long-term, larger volume data assessing neoadjuvant immunotherapy may reveal similar findings.

Immunotherapy is associated with significant immune-related adverse events that should also be highlighted. Immunotherapy-related toxicity, which can result in skin rash, colitis, hepatotoxicity and pneumonitis, has been reported in 70 to 90% of patients.[9,10] In the NICHE study, 13% of patients had grade 3 to 4 treatment-related adverse events, none of which

compromised surgery. A notable 10% anastomotic leak rate was also documented. Authors attribute this limited complication profile to the low doses and the short duration of treatment.

These data highlight the safety and preliminary efficacy of neoadjuvant chemotherapy for stage I-III dMMR colon cancers. As we wait for the phase III data to mature, immunotherapy provides an exciting new therapeutic option for patients with dMMR colon cancer.

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