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Colorectal cancer immunotherapy: a treatment quantum leap

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Surgery is the cornerstone in the treatment of non-metastatic colorectal cancer, supported by selective use of systemic chemotherapy and radiotherapy to improve distant and local control respectively. Radiotherapy has already been shown to be more effective in the neoadjuvant setting, with greater compliance than in the adjuvant setting. Recent studies have suggested this also true for systemic chemotherapy. In rectal cancer, neoadjuvant radiotherapy has led to the concept of organ preservation for tumours that respond very well. Additional neoadjuvant systemic therapy will increase the proportion of patients who do not require major surgery^{1,2}. Recent progress in immunotherapy will decrease the role of major resections in the treatment of colorectal cancer even further.

The idea of harnessing a patients' own immune system to battle cancer cells is old, with William Coley as an often-mentioned surgical pioneer who provided proof of concept as early as 1891, with injections of bacteria and bacterial toxins leading to tumour regression in patients with sarcoma. Modern cancer immunotherapy has provided modest successes in specific subsets of patients treated with cytokine therapy, cancer vaccines, and adoptive cell transfer. The unravelling of the immune checkpoint mechanism and subsequent development of immune checkpoint inhibitors (ICIs) was the real breakthrough³. Ipilimumab, an antibody that blocks cytotoxic T lymphocyte-associated protein 4, was approved for metastatic melanoma in 2011, soon followed by inhibitors of programmed cell death protein (PD) 1 and PD-L1. After establishing the role of ICI therapy in stage IV melanoma and lung cancer, it was approved as adjuvant therapy for stage III melanoma, with ongoing studies in stage III lung cancer. There is evidence from translational, preclinical, and early clinical studies to suggest that ICI therapy for micrometastatic disease is more effective with the primary tumour *in situ*, leading to a number of ongoing neoadjuvant trials in a variety of solid tumours^{4,5}. In colorectal cancer, as well as in other tumour types, response to ICIs often correlates with a high mutational burden and the presence of T cell infiltration. This is often present in the 15 per cent of non-metastatic and 5 per cent of metastatic colorectal cancers that have microsatellite instability (MSI) and deficient mismatch repair (dMMR) on histological analysis. The majority of these dMMR/MSI tumours are sporadic and 3 per cent are associated with Lynch syndrome. Younger patients with rectal cancer more frequently have dMMR/MSI tumours⁶. Mucinous tumours are associated with dMMR⁷.

ICI therapy was first approved in 2017 for dMMR/MSI metastatic colorectal cancer that progressed after first-line standard therapy, and is now also approved as first-line treatment^{8–10}. Response rates to ICI therapy in this setting vary from 31 to 69 per cent, but truly remarkable is the very long duration of the response. Adjuvant use after resection of stage III dMMR/MSI disease is currently being tested in ongoing studies. In 2017, the author's institution initiated a phase II trial of a short course of neoadjuvant ICI in early-stage colonic cancer, the NICHE study (NCT03026140: Nivolumab, Ipilimumab and COX2-inhibition in Early Stage Colon Cancer: an Unbiased Approach for Signals of Sensitivity). The early results have nicely illustrated the potential further impact of ICIs in colorectal cancer¹¹.

The NICHE study is still ongoing. Patients with non-metastatic operable tumours, both dMMR/MSI and proficient mismatch repair (pMMR)/microsatellite-stable (MSS), are eligible. In a 4-week period preceding surgery, patients receive a single dose of ipilimumab and two doses of nivolumab, and half of the pMMR/MSS group receive additional celecoxib in an effort to enhance the immune response. Toxicity is limited. A pathological response has been observed in all 20 dMMR tumours, including 12 complete responses and seven near-complete responses (less than 10 per cent residual viable tumour). A response was noted in 4 of 15 patients with pMMR tumours. There are several important observations in this small exploratory trial. The most obvious is the very high response rate among dMMR tumours, much higher than in the metastatic setting. The response in a subset of pMMR tumours, generally considered non-responsive to ICIs, strongly suggests that ICI therapy may be beneficial for a subset of early-stage pMMR tumours. The fact that a single dose of ipilimumab and two doses of nivolumab can achieve complete remission is testimony to the incredible power that lies hidden in the immune system.

What are the implications for patients with colorectal cancer, and how is this going to change the work of colorectal surgeons? Rather than determining mismatch repair status only in subgroups, aiming to identify families with Lynch syndrome, histological testing will become part of the standard diagnostic work-up for all patients with colorectal cancer. It is already relevant in patients requiring systemic therapy in a metastatic setting, and will become relevant in considering adjuvant or neoadjuvant treatment in a non-metastatic setting.

In metastatic disease, the durable responses of dMMR/MSI tumours to ICI therapy introduce a whole new dynamic. Until

recently, patients with extensive disease underwent chemotherapy with palliative intent, but patients may now have a good and durable response to ICI therapy. Some patients will have a mixed response, or oligoprogression after an initial very good response, and the role of 'adjuvant' local treatment of some remaining or progressive lesions should always be considered and discussed by the multidisciplinary team. In the author's practice, this has resulted in patients off treatment without evidence of disease for years and, with some hesitation, being considered as cured.

The next logical step is to explore (neo)adjuvant ICI therapy to eradicate micrometastatic disease in stage III dMMR/MSI tumours^{5,12}. Two randomized studies are testing adjuvant combinations of standard chemotherapy and 6–12 months of ICI. The expanded MSI cohort in the NICHE study is further exploring this goal with a short 4-week neoadjuvant course, a highly cost-efficient option with the additional potential for de-escalation of surgery. It may eventually be safe to perform less extensive resections at a time in which some advocate more extensive operations for colorectal cancer¹³.

There is a group of patients with non-metastatic locally advanced right-sided colonic cancer, with involvement of surrounding structures such as the duodenum, pancreatic head, or mesenteric vessels. They are often treated with neoadjuvant systemic therapy to increase the chances of tumour resectability. A fair proportion of these tumours is dMMR/MSI, and with the FOxTROT trial¹⁴ reporting little or no response of these lesions to neoadjuvant 5-fluorouracil/oxaliplatin, it makes much more sense to consider ICI therapy to improve resectability and outcome. Again, in the author's practice, this has resulted in marked downstaging, and complete pathological responses are not uncommon.

By far the most provocative questions raised by the NICHE study are whether and how complete responses to treatment can be detected and surgery avoided. Early standard anatomical imaging and surgical assessment during the operation cannot distinguish between residual tumour and a residual mass of mixed inflammatory infiltrate, fibrous tissue, pools of acellular mucin, and necrosis. It is only a matter of time before better diagnostic tools are developed and watchful waiting protocols are set up in specific groups of patients, guided by the experience in rectal cancer.

The management of patients with Lynch syndrome will change. This syndrome is caused by an inherited malfunction in one of the four mismatch repair genes. Extended surgery is recommended for *path_MLH1* and *path_MSH2* carriers at the time of first diagnosis of a colonic cancer¹⁵. The invasive tumours in all likelihood will respond very well to immunotherapy, but the effect on the remainder of the colon and polyps potentially has even wider implications. This could not only decrease the need for concomitant extensive resections, but also opens up possibilities for additional preventive strategies, alongside the currently studied vaccination strategy.

There are still many more questions than answers. These include optimal duration of ICI therapy, optimal timing of surgery, how to monitor responses, whether or not to combine ICI therapy with chemotherapy or radiotherapy, and whether pMMR/MSS tumours can be triggered to respond^{5,16}. From a more practical point of view, there are the hurdles of approval, accessibility, cost, and reimbursement. Having witnessed the incredible power of immunotherapy in patients with dMMR/MSI tumours, the slowness of these processes feels almost unethical. With a joint effort from clinicians, researchers, pharmaceutical companies,

and legislators, this exciting field will move forward to the greater benefit of patients.

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