Immuno-Interception for Patients with High-Risk Cancer

Asad Umar and Holli A. Loomans-Kropp

ABSTRACT

Cancer immune-interception for prevention of recurrence in patients with high-risk familial cancer like Muir–Torre syndrome or Lynch syndrome using immune checkpoint blockade inhibitors is a promising approach. Albeit, as described in a case report by Pollak and colleagues in the April 2020 issue of *Cancer Prevention Research*, it has the potential to be used as immune-interceptive with alternative dosing regimens for cancers with microsatellite instability. The combination of additional cancer preventive and immunopreventive approaches, such as vaccines and minimal dose of immune checkpoint blockade inhibitors, is another unexplored modality for cancer interception in high-risk individuals.

Muir–Torre and Turcot syndromes are rare autosomal dominant variants of Lynch syndrome, characterized by sebaceous gland and other skin tumors (such as keratoacanthomas) and an increased risk of glioblastomas, respectively. Benign sebaceous tumors and keratoacanthomas occurring in individuals with Muir–Torre Syndrome are often treated using surgical excision or cryotherapy, while the addition of chemoradiation and/or oral isotretinoin may prevent the initiation of neoplasms (1, 2). However, due to underlying germline mismatch repair defects, patients with Muir–Torre Syndrome continue to have metachronous and recurrent cancers and are therefore recommended to receive an annual colonoscopy, dermatologic examination, and follow-up care for the detection of metastasis (3).

Although the risk of cancer for individuals with Muir–Torre Syndrome, Turcot, and the more common variants of Lynch syndrome is high, these heritable diseases may offer a unique cancer interception or treatment advantage. Mismatch repair–deficient (dMMR) precancers and carcinomas bearing Lynch syndrome–associated germline mutations or sporadic *MLH1* promoter hypermethylation are highly immunogenic and may represent excellent candidates for therapies targeting the programmed cell death 1 (PD-1)/programmed cell death ligand-1 (PD-L1) immune checkpoint pathway (4). The anti-PD-1 (α-PD-1) antibodies, pembrolizumab and nivolumab, demonstrated effectiveness in patients with cancer with microsatellite instability (MSI) caused by dMMR. For instance, pembrolizumab and nivolumab showed a 31%–52% durable response in metastatic colorectal and other cancers (5, 6). In addition, an individual with Lynch syndrome presenting with colorectal and urothelial carcinomas had significant clinical benefit with dual checkpoint inhibition of PD-1/PD-L1 (7). The idea of immune surveillance for cancer prevention is further strengthened from the evidence that tumors with MSI, either due to somatic or hereditary germline mutations in DNA mismatch repair genes, have improved disease prognosis and survival over MMR-proficient tumors (8, 9).

Because of an inherent mutator phenotype and impaired DNA mismatch repair functionality, the immune response is continuously engaged, providing constant immune surveillance of lesions. The unstable nature of microsatellites, or repetitive nucleotide sequences, in the coding regions of genes leads to DNA slippage and the formation of frameshifts. The generation of these neoantigens unceasingly engages the immune response, triggering immunosurveillance and the elimination of cells with driver gene mutations, helping to keep cancer cells in check. However, at the same time, the inherent nature of the immune system is to dampen an overexuberant response, as evidenced by upregulated expression of immune checkpoint proteins, such as PD-1 and PD-L1 (10, 11). In the April 2020 issue of *Cancer Prevention Research*, Pollak and colleagues report the successful interception of cancer using an immune checkpoint blockade inhibitor (α-PD-1) in a patient with Muir–Torre Syndrome, the result of a highly penetrant germline *MSH2* mutation. This case represents a typical Muir–Torre Syndrome clinical picture: a patient developing hundreds of neoplasms ($n = 136$) over 18-year period before current interventions that eventually intercepted and prevented the high-risk cancer progression. Consequently, chemoradiotherapy followed by 1 year of immunotherapy with pembrolizumab was administered. The significant toxicity that is usually observed with chemoradiotherapy was reported and managed symptomatically; however, the immunotherapy regimen was well-tolerated. The patient remained free of both premalignant and malignant neoplasia 1 year after completing immunotherapy. This is an especially remarkable example of

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Cancer Prev Res 2020;13:493–6

doi: 10.1158/1940-6207.CAPR-20-0136

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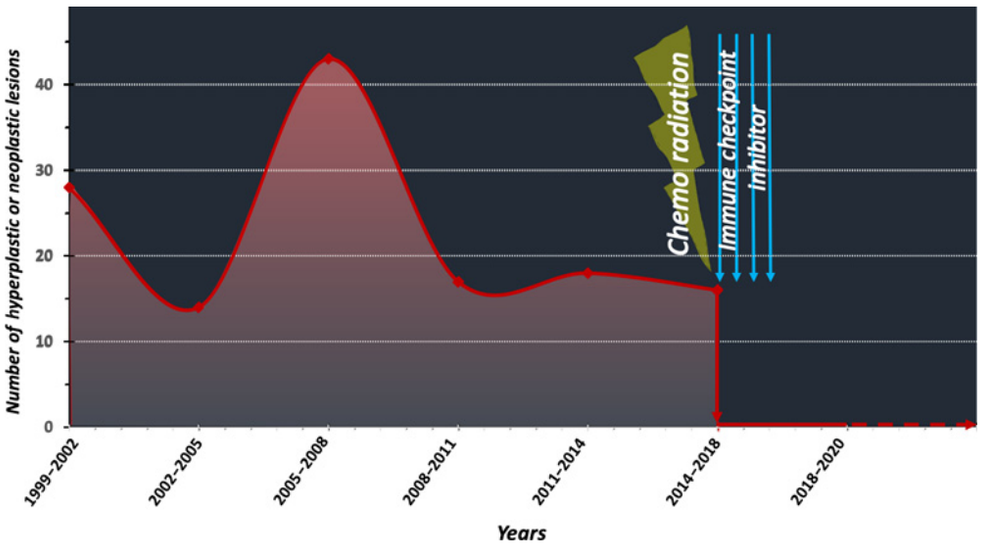

Figure 1.
Immuno-interception for patients with high risk cancers.

cancer immune interception, as both precancerous lesions and cancer recurrence was stopped in its tracks. As noted by the authors, a major concern when using an immune checkpoint blockade strategy for long-term use in conditions such as Lynch syndrome or other variants of dMMR is the associated toxicities. Although it remains to be tested in randomized clinical trials, immune checkpoint inhibitors for cancer interception may prevent recurrence in similar high-risk cancer populations, especially in microsatellite unstable cancers. Yet, several issues will need to be resolved, including duration, frequency, and the optimal therapeutic combination to provide maximum benefit with minimal risk of toxicity. It is possible that a lower dose, a pulsed approach, or the addition of proven cancer preventives, for example, aspirin or NSAIDs, in these high-risk individuals could effectively intercept and/or prevent recurrent and concurrent cancers of multiple organs (**Fig. 1**).

Based upon data suggesting the value of immune checkpoint blockade therapy for cancers with MSI, the patient with Muir–Torre Syndrome with an *MSH2* mutation responded extremely well to chemoradiation and immune checkpoint blockade inhibition, substantially intercepting disease progression and preventing recurrence. As demonstrated by Pollak and colleagues, the potential efficacy of immune-interception, halting late-stage disease and preventing the progression of premalignant lesions, is novel and significant to the field of cancer immunotherapy and immunoprevention. Others have reported that Muir–Torre Syndrome benign lesions have lost mismatch repair function, show MSI (12), and, by inference, upregulated PD-1/PD-L1 overexpression. This provides a rationale for the utility of this treatment paradigm in other Lynch syndrome variants that exhibit MSI for cancer immuno-interception. In the absence of immune checkpoint inhibitors, the trajectory of the Muir–Torre Syndrome patient's disease would likely have risen and been difficult to manage (**Fig. 1**). It remains unknown whether chemoradiation or other cancer preventive combinations, such as aspirin or NSAIDs, may also be needed, or could even be synergistic, in managing disease progression. Furthermore, it is possible other immune response modulators with lower toxicity, in combination with NSAIDs, will keep overall disease burden low and, potentially, inhibit the malignant transformation of precancerous lesions. Needless to say, despite the excellent clinical response to immune checkpoint inhibitors observed in a single patient, utilizing immune-interception as a practical strategy requires considerably more research and a better understanding of the best regimen to optimize patient benefit for high-risk individuals, especially those with inherited defects in DNA mismatch repair genes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received March 24, 2020; revised March 30, 2020; accepted April 3, 2020; published first May 19, 2020.

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Cancer Prev Res 2020;13:493-496.

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