Neoadjuvant Immunotherapy: Is this the new Hope in Mismatch-Repair Deficient Locally Advanced Rectal Cancer?

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Abstract

Neoadjuvant chemotherapy and radiation followed by surgical resection of the rectum is a standard treatment for locally advanced rectal cancer. Approximately 5-10% of rectal adenocarcinomas are mismatch-repair deficient (dMMR). These tumours respond poorly to standard chemotherapy regimens, including neoadjuvant chemotherapy in locally advanced rectal cancer. Programmed cell death inhibitors including Dostarlimab and Toripalimab alone or in combination with Celecoxib, offer promising results in the treatment of dMMR locally advanced rectal cancer.

Keywords: Dostarlimab, Immunotherapy, PD-blockade, Toripalimab.

Cancer of the rectum is the third-most incident cancer globally with nearly 44,850 (26,650 men and 18,200 women) new cases of rectal cancer predicted in 2022.[1] Adenocarcinoma accounts for 90% of rectal cancer histologic types; the rest include neuroendocrine, signet ring, squamous cell, adenosquamous, small cell and undifferentiated carcinomas. Neoadjuvant chemotherapy and radiation followed by surgical resection of the rectum is the standard treatment for locally advanced rectal cancer.

Approximately 5-10% of rectal adenocarcinomas harbour deficient mismatch repair (MMR) DNA. MMR deficiency is one of the best-understood forms of genetic instability and is characterized by the loss of function of the MMR pathway. Failure to repair replication-associated errors due to a defective MMR system allows the persistence of mismatch mutations all over the genome which may lead to cancer. MMR deficiency is most common in colorectal cancer as also in gastrointestinal and endometrial cancer, but it may also be found in cancers of the breast, prostate, bladder, and thyroid. MMR deficiency may also be found in an inherited disorder called Lynch syndrome (previously known as hereditary non-polyposis colorectal cancer syndrome). These tumours respond poorly to standard chemotherapy regimens including neoadjuvant chemotherapy in locally advanced rectal cancer.[2] Knowing if a tumour is MMR deficient (dMMR) may help plan treatment or predict how well the tumour will respond to treatment.[3]

In August 2021, US Food and Drug Administration (FDA) approved Dostarlimab (Jemperli®, Glaxo SmithKline), a programmed cell death receptor-1 (PD-1) blocking antibody, for the treatment of adult patients with mismatch-repair deficient (dMMR) recurrent or advanced solid tumours (as determined by an FDA approved test) and which show no response to prior treatment and are left with no satisfactory alternative treatment modalities. The approval of Dostarlimab follows an FDA priority review of the Biologics License Application and is based on the collective results from the dMMR endometrial cancer cohort A1 and the dMMR solid-tumour (non-endometrial cancer) cohort F of the ongoing GARNET trial. The GARNET trial was a multicentre, non-randomised, multiple parallel-cohort, open-label study which began in March 2016 and continued till August 2019. Cohort F included patients with dMMR recurrent or advanced non-endometrial cancers, with the highest prevalence in colorectal, small intestine and stomach cancers. Patients received 500mg Dostarlimab by intravenous route every 3 weeks for 4 cycles, and then 1000 mg every 6 weeks. This treatment was associated with clinically meaningful anti-tumour activity with an acceptable safety profile. Based on the benefits seen in the context of metastatic disease in the GARNET trial, the study team hypothesised that single-

agent PD1 blockade might be beneficial in dMMR locally advanced rectal cancer.[4] This triggered an interest in PD-1 blockade to be used as a single agent of dMMR tumours. In dMMR rectal tumours, immune checkpoint blockade alone is highly effective as a first-line treatment, as well as in the treatment-refractory disease, with objective response rates of 33-55%, clinically significant duration of response, and prolonged overall survival.

Neoadjuvant immunotherapy has also been investigated in solid tumours, including those that are known to be sensitive to checkpoint blockade in metastatic diseases like non-small cell lung cancer, urothelial carcinoma and melanomas.[5,6] In a study done on non-small cell lung cancer (NSCLC) patients, it was observed that two doses of PD-1 blockade resulted in a 10% response rate. In another study involving melanoma patients, a 52% response rate was seen with immunotherapy alone.[7]

Another study shows that a single dose of Ipilimumab and two doses of Nivolumab before surgery in dMMR colon cancer resulted in a 50% response.[8] Toripalimab alone or in combination with celecoxib resulted in an imaging-based response in 55% of patients.[9] It has also emerged that a longer course of immunotherapy showed better response compared to shorter exposure to checkpoint blockade as a response to immunotherapy takes months rather than weeks to evolve. A recent study by Cercek, *et al* done on 12 patients of dMMR rectal cancer showed that treatment with Dostarlimab, given every 3 weeks for 9 cycles over 6 months, revealed 100% response.[10] This could be a breakthrough in the treatment of rectal cancers as these patients have been seen to have more than 1-year of sustained clinical response without any need for further surgery or chemotherapy. This would save the patients from the associated side effects of bowel, bladder, sexual dysfunction and the hassles of a diverting colostomy. Thus, neoadjuvant immunotherapy has undoubtedly emerged as a potential primary intervention in dMMR locally advanced rectal tumours.

Still, the question of why the localized dMMR rectal tumours respond so well with PD-1 blockade as compared to metastatic colorectal cancer remains to be answered. The probable explanation could be the gut microbiome's influence in the evolution of antitumour response potentiated by immune checkpoint blockade.[11] Certain bacterial species like *Fusobacterium nucleatum* were seen to be associated with an immune-responsive environment in mismatch-repair tumours. *Ruminococcus spp.* and *Akkermansia spp.* of gut are associated with notable pathological responses in NSCLC.[12] Thus we can hypothesize that in addition to the burden of mutation defect associated with mismatch-repair deficiency, the gut-microbiome also has a role to play in eliciting a good clinical response in such tumours.

On the whole, neoadjuvant immunotherapy involving PD-1 blockade along with the influence of the gut microbiome could drastically improve the patient response and survival in locally advanced rectal cancer patients with mismatch repair deficiency. PD-1 blockade with Dostarlimab for 6 months is a promising candidate for complete remission in locally advanced rectal cancer saving the patients from the adverse effects of chemoradiation and surgery. However, this study needs to be followed up for a longer period in a larger cohort to come to a definite conclusion asserting its 100% response. Taken together, neoadjuvant immunotherapy with agents such as Dostarlimab could turn out to be a beacon of hope for such patients in providing the best response with minimal side effects.

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IMAGE QUIZ ANSWER

The child is suffering from a modified superficial dermatophytosis known as 'Tinea pseudoimbricata' or 'Tinea indecisiva'. It forms a subset of 'Tinea incognito', or altered tinea, where the typical features of central clearing, peripheral scaling and inflammatory border are absent or reduced. It is characterized by multiple concentric rings with variable scaling. The lesions are similar to Tinea imbricata, which is caused by *Trichophyton concentricum*. On the other hand, Tinea pseudoimbricata has been shown to be caused by multiple dermatophyte species including *Trichophyton tonsurans*, *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Microsporum audouinii* and *Microsporum gypseum*.

Tinea pseudoimbricata is a presentation seen in immunocompromised individuals and in patients with history of topical steroid abuse.[1-3] It presents with sequentially appearing concentric scaly rings, giving rise to the characteristic "ring-within-a-ring appearance".[4] A high index of clinical suspicion and direct microscopic examination of skin scrapings with KOH and fungal culture on Sabouraud's dextrose agar (SDA) are vital for the diagnosis.

The condition necessitates systemic antifungal therapy for a prolonged period of at least 6-8 weeks. The drugs recommended are terbinafine and itraconazole. Suboptimal response is expected with fluconazole or griseofulvin. The prognosis is good with adequate and prolonged treatment coupled with management of causes of immunosuppression. This is commonly in the form of topical or systemic steroid abuse, which needs to be stopped. The same was denied in our case. Other causes like HIV infection, like in our case, need to be managed adequately. At the same time, it is important to treat the family members and educate them regarding the infectious nature of the condition, the role of fomites like clothing and bedding, separate washing of infected clothes, avoidance of sharing of towels, clothes, bed linen, and soaps, and the need for good skin hygiene practices.

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