EDITORIAL

DOSTARLIMAB: A BEACON OF HOPE FOR CANCER PATIENTS

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Colorectal cancer is ranked as the fourth most prevalent cancer in the world and second leading cause of cancer related deaths in the United States. According to WHO, approximately 875,000 new cases are encountered worldwide per year and accounts for 8.5% of all new cases of cancer. Males are highly predisposed to rectal cancer compared to females as its incidence in males ranges from 48.3 to 72.5 per 100,000 per year while it ranges from 32.3 to 56 per 100,000 per year in females. The same trend is seen in Pakistani male population.[1,2] Approximately 18% of rectal cancers have early onset; age less than 50 years. Obesity, increased red meat consumption, cigarette smoking, low fruits and low vegetable consumption and low physical activity are associated with an increased risk of developing colorectal cancer.[3] Pathophysiological process of normal rectal epithelium to precancerous cells (adenomas) and finally to invasive carcinomas occurs as a result of genetic mutations which are either acquired (somatic) or inherited (germline). Evidence suggests that adenomatous polyps that acquires dysplastic changes over a period of 10 to 15 years leads to development of invasive carcinomas. The main molecular pathways which are linked to CR cancer development are mismatch repair, hyper methylation and chromosomal instability. Ninety percent of all rectal carcinomas are adenocarcinomas while the remaining less common types are spindle squamous, adenosquamous and undifferentiated. The most appropriate treatment is determined by accurate staging of rectal carcinoma. Different treatment options are available such as endoscopic resection, neoadjuvant therapy, surgical resection, systemic therapy, cytotoxic chemotherapy, VEGF inhibitors, Anti-EGFR Monoclonal Antibodies and immune check point inhibitors.[4] The standard treatment for locally advanced rectal cancer is neoadjuvant chemotherapy and radiation which is then followed by surgical resection.[5] Check point inhibitors, specifically anti PD-1/ PD-L1 interaction are becoming a new line of research for the treatment of colorectal cancers. After the successful effects of anti PD-1 for renal cell carcinoma, non-small cell lung cancer and melanoma, several RCT's are conducted on effects of immune therapy of anti PD-1 on colorectal cancers. The PD-1 immune checkpoint negatively regulates the activation of T cell in order to maintain peripheral tolerance. Tumor cells expressing PD-1 ligands on their surface induces the state of immunosuppression and prevents the activation of T cells. Anti PD-1 monoclonal antibodies blocks ligand binding to PD-1 and hence reactivates the T cells to act against the tumours.[6] A breakthrough in the treatment of cancer and specifically rectal cancer was highlighted recently in a study published in the 'The new England Journal of Medicine' the results of phase 2 trial demonstrated that Dostarlimab, an anti-PD-1 monoclonal antibody had shown a 100% clinical complete response rate among a small cohort of patients with mismatch repair-deficient locally advanced rectal cancer. In the study twelve patients (median age, 54-years) with mismatch repair-deficient stage-II and stage -III rectal adenocarcinoma received Dostarlimab every 3 weeks for 6 months followed by a 6-months follow up. This treatment was followed by standard chemo radiation and surgery and had a complete clinical response, showing no evidence of tumor cells on MRI, fluorodeoxyglucose-positron-emission tomography, endoscopic evaluation and digital rectal examination. Till this time there is no case reported of progression or recurrence or any side effects.[5] Given the remarkable response of 100% treatment with PD-1 blockade, Dostarlimab may replace the current standard of care for locally advanced rectal cancer. This could be one of the most important breakthroughs in medical history but requires further studies of longer duration with increased number of participants and regular follow ups after different time intervals.

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This editorial may be cited as: Sahibzada AH, Ihsan F. Dostarlimab: a beacon of hope for cancer patients. Rehman J Health Sci. 2022;4(2). 71-2

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